Aspects of blood pressure and lipid lowering drug treatment in individuals stratified by absolute cardiovascular disease risk

by

Chau Le Bao Ho

BMed

Menzies Institute for Medical Research

Submitted in fulfilment of the requirements for the Doctor of Philosophy (Medical Research)

University of Tasmania, June 2019

Declaration of originality

The research work presented in this thesis was supervised by:

Primary supervisor

Professor Mark Raymond Nelson, PhD

Menzies Institute for Medical Research

University of Tasmania,

Hobart, Australia

Co-supervisor

Dr Monique Breslin, PhD

Menzies Institute for Medical Research

University of Tasmania,

Hobart, Australia

Co-supervisor

Professor Jenny Doust, PhD

Centre for Research in Evidence-Based Practice

Bond University

Brisbane, Australia

Co-supervisor

Professor Christopher Reid, PhD

Monash Centre of Cardiovascular Research and Education in Therapeutics

Monash University

Melbourne, Australia

Department of Health Policy and Management

Curtin University

Perth, Australia

Declaration of Originality

"This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright".

Name: Chau Le Bao Ho

Signed: ……. Date: 29/05/2019

Statement of authority of Access

This thesis may be made available for loan and limited copying and communication in accordance with the Copyright Act 1968.

Name: Chau Le Bao Ho

Signed: …… Date: 15/11/2019

Statement regarding Published Work contained in Thesis

The publishers of the papers comprising Chapters 2, 3 and 5 hold the copyright for that content, and access to the material should be sought from the respective journals. The remaining non published content of the thesis may be made available for loan and limited copying and communication in accordance with the Copyright Act 1968.

Name: Chau Le Bao Ho

Signed: …… Date: 15/11/2019

Statement of co-authorship

This thesis includes four papers, in which Chau Le Bao Ho (CLBH) is not the sole author. CLBH took the lead in this research. She designed the studies, collected data archives, performed analyses, interpreted the findings and prepared the manuscripts, with contributions from the co-authors.

The following people and institutions contributed to the publication of work undertaken as part of this thesis:

Chau Le Bao Ho (candidate) – Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia.

Mark Raymond Nelson (primary supervisor) - Menzies Institute for Medical Research, University of Tasmania, Hobart and CCRE Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Monique Breslin (co-supervisor) - Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia.

Jenny Doust (co-supervisor) - Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia.

Christopher M. Reid (co-supervisor) - School of Public Health, Curtin University, Perth and CCRE Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Enayet K. Chowdhury (co-author) - School of Public Health, Curtin University, Perth and CCRE Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Barry R. Davis (co-author) - University of Texas School of Public Health, Houston, United States.

Lara M. Simpson (co-author) - University of Texas School of Public Health, Houston, United States.

Sharon Sanders (co-author) - Centre for Research in Evidence-Based Practice, Bond University, Gold Coast, Australia.

Frank P. Brouwers (co-author) - Department of Cardiology, Haga Teaching Hospital, Postbus 40551, LN the Hague, The Netherlands.

Rudolf A. de Boer (co-author) - Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

The contributions of each of the authors are detailed as follows.

Chapter 2

Ho CLB, Breslin M, Doust J, Reid CM & Nelson MR. (2018). Effectiveness of blood pressure-lowering drug treatment by levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study. BMJ Open, 8(3), e017723.

The contributions of each author are as following:

- CLBH was the primary author and contributed approximately 80% to study design, data extraction, data analyses, interpretation of results, and manuscript preparation.
- MB contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- JD contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- CMR contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- MRN contributed to the study design, data archive from the Australian Data Archive, statistical analyses, interpretation of results, critical revision of the manuscript and final approval.

Chapter 3.

Ho CLB, Breslin M, Chowdhury EK, Doust J, Reid CM, Davis BR, Simpson LM & Nelson MR. (2019). Legacy effect of baseline blood pressure 'treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Plan to submit to Journal of Hypertension.

Statement of co-authorship

The contributions of each author are as following:

- CLBH was the primary author and contributed approximately 70% to study design, data analyses, interpretation of results, manuscript preparation.
- MB contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- EKC contributed to interpretation of results, revision of manuscript and final approval.
- JD contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- CMR contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- BRD contributed to data collection and extraction of ALLHAT, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- LMS contributed to data collection and extraction of ALLHAT, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- MRN contributed to the study design, data archive from the ALLHAT principle investigator, statistical analyses, interpretation of results, critical revision of the manuscript and final approval.

Chapter 4

Ho CLB, Sanders S, Doust J, Breslin M, Reid CM, Davis BR, Simpson LM, Brouwers FP, Boer RA & Nelson MR. (2019). Legacy effect of delayed blood pressure lowering drug treatment in middle-aged adults with mildly elevated blood pressure: systematic review and meta-analysis. Plan to submit to Journal of Hypertension.

The contributions of each author are as following:

- CLBH was the primary author and contributed approximately 60% to study design, data archive from the PREVEND-IT and ALLHAT principle investigators, the search for eligible studies, screened the results of the

search data extraction, data analyses, interpretation of results, manuscript preparation.

- SS conducted the search for eligible studies, screened the results of the search, data extraction, data analyses, interpretation of results, manuscript preparation
- JD contributed to data extraction, data analyses, interpretation of results, revision of the manuscript and final approval
- MB contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- CMR contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- BRD contributed to data collection and extraction of ALLHAT, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- LMS contributed to data collection and extraction of ALLHAT, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- FPB contributed to data collection and extraction of PREVEND-IT, interpretation of results, revision of the manuscript and final approval.
- MRN contributed to the study design, statistical analyses, interpretation of results, critical revision of the manuscript and final approval.

Chapter 5

Ho CLB, Chowdhury EK, Breslin M, Doust J, Reid CM, Wing LMH & Nelson MR. (2019). Short-and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study. Journal of clinical lipidology, 13(1), 148-155.

The contributions of each author are as following:

- CLBH was the primary author and contributed approximately 70% to study design, data analyses, data extraction, interpretation of results, manuscript preparation.
- EKC contributed to study design, data analyses, data extraction, interpretation of results, revision of the manuscript and final approval.

Statement of co-authorship

- MB contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- JD contributed to statistical analyses, interpretation of results, revision of the manuscript and final approval.
- CMR contributed to study design, data collection of ANBP2, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- LMHW contributed to data collection of ANBP2, statistical analyses, interpretation of results, revision of the manuscript and final approval.
- MRN contributed to the study design, statistical analyses, interpretation of results, critical revision of the manuscript and final approval.

We the undersigned agree with the above stated “proportion of work undertaken” for each of the above published (or submitted) peer-reviewed manuscripts contributing to this thesis:

Signed:	
Professor Mark Nelson	Professor Alison Venn
Supervisor	Head of School
Menzies Institute for Medical Research	Menzies Institute for Medical Research
University of Tasmania	University of Tasmania
Date: 31/5/19	

Statement of ethical conduct

The research incorporated in this thesis complied with the 'Australian Code for the Responsible Conduct of Research' and 'National Statement of Ethical Conduct in Human Research'**.** The Tasmania Human Research Ethics Committee (HREC) approved this project (approval number H0015252).

Name: Chau Le Bao Ho

Signed: …… Date: 29/05/2019

Acknowledgements

First of all, I wish to express my sincere thanks to my supervisors Professor Mark Nelson, Dr Monique Breslin, Professor Jenny Doust and Professor Christopher Reid. I am profoundly grateful to my 'teacher', Professor Mark Nelson for his patience, constant supports and detailed guidance. Teacher, I appreciate every moment with you and your family, particularly Jan, all of you made me feel like a part of your family and that helped me go through the first days of being away from home. I would like to thank Dr Monique Breslin for her substantial support on statistics. She is a very nice instructor who could spend hours with me to explain my concern regarding statistics, even if some of them were basic questions. I wish to thank Professor Jenny Doust and Professor Christopher Reid for their supports and encouragements. When we first met in person, I was very impressed with the warm welcome from Jenny and Chris. My big thanks to all of my supervisors, all of their instructions or comments helped me become more confident and grow up throughout this journey.

Also, my project would have not been completed without the contribution of participants and the research teams of the ANBP, ANBP2, ALLHAT and PREVEND-IT trials, special thanks to Professor Lindon Wings, Professor Barry Davis, Professor Frank P. Brouwers and Professor Rudolf A. de Boer for their supports and acceptances for using data of these trials in my projects. Also, I wish to thank Dr Enayet Karim Chowdhury, Dr Lara M Simpson and Dr Sharon Sanders for their substantial contributions on the analysis related to the ANBP2, ALLHAT trials and the systematic review and meta-analysis.

Thanks to the research coordinators Prof Costan Magnussen, Prof Heinrich Korner, Prof Wendy Oddy, Stewart Wells, Joanne McEvoy (funding officer) and other Menzies staffs for your understanding, kind helps and supports.

My sincere thanks to Dr Quan Huynh and his parents (Dr Son Huynh and Dr Chau Le) who inspired and encouraged me to start the PhD journey in Menzies. I would like to thank my beloved friends who made my journey more

colourful and relaxing. Thanks for treating and caring me like a family member. Being with you helped refresh my mind and kept me optimistic.

Last but not least, my family is always an important part of my life. Thank you, my dear parents, for your unconditional love and support. Studying abroad made me deeply understand the value of a family. Mom, I really missed your complaints and reminders that used to make me annoyed.

I am very grateful to have the presence of all of you in my PhD journey that contributed to an unforgettable part of my life and has helped me to become the person who I am today.

Financial acknowledgements

I greatly appreciate the financial support from the Merle Weaver Postgraduate Scholarship for substantial supports on the tuition fee and living expense for my PhD. Also, I am grateful to the RACGP foundation and the Therapeutic Guidelines Ltd for their support on this project.

Table of contents

Table of contents

List of tables

List of figures

List of abbreviations

AASK	The African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood pressure Control in Diabetes trial
ACC/AHA	American College of Cardiology/American Heart Association
ACE-I	Angiotensin Converting Enzyme Inhibitors
ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AF	Atrial Fibrillation
ALLHAT-LLT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial
ANBP	Australian National Blood Pressure study
ARB	Angiotensin II Receptor Blockers
Benedict	The Bergamo Nephrologic Diabetes Complication Trial
BP	blood pressure
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular disease
CVE	Cerebrovascular event
DBP	Diastolic blood pressure
DHP-CCB	Dihydropyridine Calcium Channel Blocker
DM	Diabetes Mellitus
ESC	European Society of Cardiology
FH	Familial Hypercholesterolemia
HDL-c	High Density Lipoprotein cholesterol
HF	Heart failure
HOPE	Heart Outcome Prevention Evaluation
JBS	Joint British Societies
LDL-c	Low Density Lipoprotein cholesterol
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction

List of abbreviations

MRC	Medical Research Council trial
MRC-TMH	The Medical Research Council trial of treatment of mild hypertension
NA	Not Applicable
NHF	National Heart Foundation
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal anti-inflammatory drugs
NVPDA	National Vascular Disease Prevention Alliance
PREVEND-IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial
PROSPER	Pravastatin in elderly individuals at risk of vascular disease trial
PVD	Peripheral Vascular Disease
RF	Risk factor
RR	Risk Ratio
SBP	Systolic blood pressure
SD	Standard Deviation
SHEP	Systolic Hypertension in the Elderly Program trial
SIGN	Scottish Intercollegiate Guidelines Network
SOLVD-Prevention	The Studies of Left Ventricular Dysfunction
SYST-Eur	Systolic Hypertension in Europe Trial
TC	Total Cholesterol
TG	Triglyceride
TIA	Transient Ischemic attack
TOD	Target Organ Damage
TOMHS	Treatment Of Mild Hypertension Study
TZ	Thiazide or thiazide-like diuretics
UKPDS	The UK Prospective Diabetes Study
USPHS	The United States Public Health Service Hospitals Intervention Trial
USPSTF	US Preventive Services Task Force

List of abbreviations

VA	The Veteran Administration
VA-NHLBI	Veterans Administration-National Heart, Lung, and Blood Institute trial

Abstract

Background

Primary prevention of cardiovascular disease (CVD) based on an absolute risk approach is more cost-effective than the traditional individual risk factor approach based on blood pressure (BP) or lipid thresholds alone. Although BP lowering drug treatment is recommended in high-risk individuals even for those below traditional BP thresholds (e.g. <140/90 mmHg) in many guidelines, withholding BP lowering drug in individuals with mildly elevated BP and low-moderate risk is controversial as it is contrary to historical recommendations and there are concerns regarding legacy effects. Similarly, lipid-lowering drug treatment (LLT) is widely prescribed in high-risk individuals based on evidence from large randomised controlled trials. However, these trials lacked elderly participants who are at high baseline risk due to their age. The effects of lipid-lowering drug treatment in the healthy elderly remain unclear.

Aim

To investigate the effect of BP and LLT on short- and long-term mortality outcomes stratified by absolute CVD risk.

Methods:

Two post-hoc observational studies of the Australian National Blood Pressure study (ANBP), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and a systematic review and meta-analysis were conducted to investigate the effects of BP lowering drug treatment in individuals stratified by absolute CVD risk on short- and long-term outcomes. ANBP was a community-based randomised placebo-controlled trial in 'mild hypertension' defined as diastolic BP ranging from 95-109 mmHg and systolic BP lower than 200 mmHg conducted in Australia in the 1970s. ALLHAT was a double-blind, randomised active-controlled trial conducted in multiple centres in North America that included participants with untreated systolic BP lower than 180 or treated systolic BP lower than 160 mmHg. Based on the BP treatment status at baseline, participants were re-stratified to 'treatment naïve'

and ‘previous treatment’ group. The systematic review and meta-analysis included randomised controlled trials with a post-trial phase and which enrolled participants who were middle-aged and had mildly elevated BP. Similarly, to investigate the effects of LLT in the elderly, a post-hoc observational study on the Second Australian National Blood Pressure study (ANBP2) was conducted that re-stratified participants into ‘LLT’ and ‘no LLT’ group based on their treatment status at baseline. All four studies excluded participants with previous CVD events. Treatment effects were estimated by hazard ratio with 95% confidence interval (CI) using a Cox proportional hazard model. Subgroup analyses by baseline estimated CVD risk score were performed.

Results

Generally, the three studies on the effects of BP lowering drug treatment did not record any clinical harms as a result of delayed drug treatment in low-moderate risk individuals or in middle-aged adults with mildly elevated BP. The post-hoc study on the ANBP population (median follow-up 4.4. years) observed a substantial beneficial effect of BP lowering drug treatment regarding absolute risk reduction in any trial endpoint, all-cause mortality and major CVD events in the highest risk tertile group, whereas the low or moderate risk tertile was unlikely to benefit. In the ALLHAT trial with a longer follow-up period (up to 14.1 years), delayed BP lowering drug treatment was not associated with any significantly increased risk of all-cause or CVD mortality at any level of CVD risk stratification when drug therapy was closely monitored by a clinician. Similarly, in the systematic review and meta-analysis in middle-aged adults with mildly elevated BP, we found non-significant effects of delayed BP lowering drug treatment in short- and long-term all-cause and CVD mortality regardless of the CVD risk stratification. In the study looking at the effects of LLT in those aged 65 years or over stratified by absolute CVD risk, LLT was associated with a reduced long-term all-cause mortality suggesting that the mortality benefit of LLT for the elderly may take longer to become evident at any level of CVD risk. High-risk participants also obtained further benefits for short-term all-cause mortality.

Conclusions

In terms of the effects of BP lowering drug treatment, our analysis provides further justification that an absolute risk strategy is superior to management based on the BP level alone in identifying those who are most likely to benefit from drug therapy. The results support using absolute CVD risk to determine when to initiate BP lowering drug treatment for primary prevention of CVD. These studies found no long-term adverse risk of all-cause or CVD mortality in low-moderate risk individuals or middle-aged adults with mildly elevated BP, thus partly addressing clinician concerns of 'legacy effects' when BP lowering drug therapy is delayed. In contrast, LLT in the elderly may require long-time follow-up (e.g. 10 years) to become evident.

Chapter 1

Introduction

Chapter 1 Introduction

Definition of cardiovascular disease (CVD) used in current guidelines

CVD refers to a group of disorders related to the heart and blood vessels. The use of the CVD term differs slightly between various organisations. Fundamentally, CVD includes 'hard' coronary heart disease (myocardial infarction and fatal coronary heart disease) and 'hard' cerebrovascular disease (non-fatal and fatal stroke) [1-5]. In addition, CVD in some guidelines [1-3, 5] incorporate angina, heart failure, peripheral vascular disease or transient ischemic attack.

The burden and trend of CVD

Global

Over the past decade, CVD remains the dominant burden of disease worldwide. According to the Global Burden of Disease study 2015 [6, 7], approximately one-third of all deaths (18 million) worldwide were attributable to CVD and was projected to exceed 24 million by 2030 [8]. Coronary heart disease (CHD) and stroke were the two most common causes of CVD mortality and accounted for 85% (15.2 million) of CVD deaths (15.2 million) [6]. Also, the prevalence of CVD increased by 25% from 2005 to 2015, with the highest prevalence recorded in sub-Saharan Africa, Eastern Europe, and Central Asia [7]. CVD is no longer limited to high-income countries. It has shifted to low-middle income countries (LMI) and now accounts for 80% of global CVD deaths [9], a so-called "epidemiologic transition" [10] (Figure 1.1).

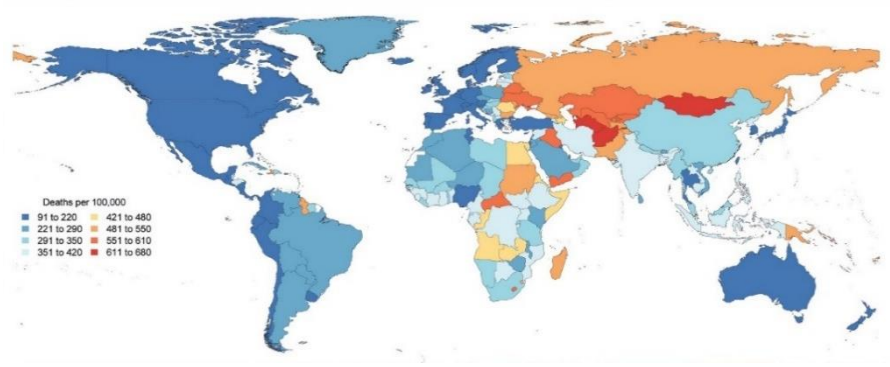


Figure 1.1 Global Map, Age-Standardized Death Rate of CVD in 2015

Figure adapted from Roth et al[7]. Journal of the American College of Cardiology 2017;70(1):1-25.

The “epidemiologic transition” is characterised by five main stages (i.e. age of pestilence and famine, age of receding pandemics, age of degenerative and man-made diseases, age of delayed degenerative diseases and age of health regression and social upheaval) with different geographic areas [10]. While regions at stage 1 such as Sub-Saharan Africa, rural India and South America have mainly suffered from rheumatic heart disease, infection and nutritional cardiomyopathies, countries at stage 2 (e.g. China) have experienced said diseases and additionally hypertensive heart disease and haemorrhagic stroke. Stage 3 and stage 4 are primarily represented by strokes and ischemic heart disease. However, the diseases occurred mostly in young people in areas at stage 3 (Urban India, former socialist economies, aboriginal communities), whereas areas at stage 4 (Western Europe, North America, Australia, New Zealand, etc.) observed a delayed degenerative disease in the older population. While the progress from stage 1 to stage 4 indicates a positive health development, countries in stage 5 (e.g. Russia) have witnessed a social catastrophe with the re-emergence of rheumatic heart disease, infection, alcoholism, violence; ischaemic and hypertensive disease in the young.

Low-middle income countries (LMI)

In recent years, LMI countries have been heavily impacted by globalisation, urbanisation and industrialisation more than ever before [11]. This progress has led to changes in behaviour and lifestyle, called ‘westernisation’.

This phenomenon was characterised by the increased consumption of high-energy, salted and high saturated food and a decrease in physical activity [12, 13]. In addition, the decrease in premature deaths from infectious and nutrition disease has improved life-expectancy in LMI countries thus increasing the number of people in middle and old age where CVD is more prevalent, with accumulative risk factors from childhood to early adulthood. In the period 1990-2013, the number of CVD-related deaths increased by 66% (from 7.2 million to 12 million) in LMI countries [14]. Due to the relatively young age structure, CVD affected a larger number of working-age adults that contributed to increasing the cost of CVD to the relevant communities. As reported in the PURE study [15](Prospective Urban-Rural Epidemiology) the risk factor burden estimated by INTERHEART risk score in LMI countries was lower than the corresponding in high-income countries, although the incidence and mortality were higher. Thus, not CVD RFs, but other determinants associated with healthcare systems and services, treatment strategy, education level dominantly contributed to the CVD burden in the developing world. As estimated by the World Health Organisation, more than 50% (US$3.76 trillion) of economic loss of non-communicable disease would be attributable to CVD in the period 2011-2025 (Figure 1.2) [16].

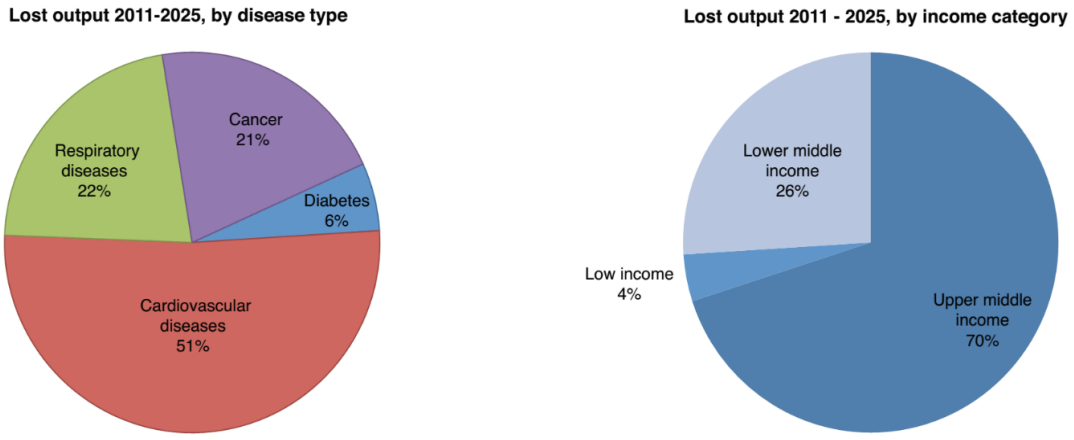


Figure 1.2 Non-communicable disease cost by disease and income levels in Low-middle income countries.

Figure adapted from the World Health Organization and World Economic Forum. From Burden to “Best Buys”: Reducing the Economic Impact of NCDs in Low and Middle-Income Countries. Geneva, Switzerland: WHO; 2011[16]

High-income countries

Since the peak level in the early 1970s, the mortality and incidence of CHD and stroke significantly declined by up to 50% in high-income countries (e.g. Australia, Canada, France, Japan, the United Kingdom and the United State) [17-22]. This achievement mainly resulted from the reduction in CVD risk factors and an improved treatment strategy[21-26]. However, in the last 25 years (1990-2015), this improvement has slowed or even plateaued [7]. In the UK from 1996 to 2005, age-standardised incidence and mortality from CHD annually decreased by approximately 2% and 4% respectively, but the age-standardised prevalence increased by about 1.5% [27]. As a global phenomenon, ageing contributed to the increased prevalence of CHD and stroke, and the cost of medical expenditure throughout a lifetime course increased correspondingly [20, 27, 28]. In the US, direct (medical) and indirect (lost-productivity) cost of CVD was US$555 billion in 2015 and was projected to increase to $1.1 trillion by 2035 [29].

CVD is likely to remain a leading cause of death in both developed and developing worlds in the next few years [30-33].

Primary prevention of CVD

Primary prevention of CVD aims at reducing the development of CVD risks to prevent the occurrence of a first CVD event in 'healthy' individuals without clinically established CVD [26, 34]. A first CVD event may be either a non-fatal or fatal event and up to 80% of premature CVD defined as premature CVD in the young is preventable [35]. Primary prevention strategies focus on delaying the first CVD events, prolonging symptom-free life and reducing CVD mortality at diagnosis. Current primary prevention programs recommended by guidelines regarding population level or individual level are cost-effective [36].

Absolute CVD risk for primary prevention of CVD

As major CVD risk factors cluster and interact together, moreover blood pressure (BP) and blood cholesterol have a continuous effect on CVD risk, a so-called 'normal' BP (systolic BP< 140 mmHg and diastolic BP < 90 mmHg) or a 'normal' blood lipid (total cholesterol (TC)<6.5 mmol/L) does not exclude an individual from increased CVD risk [49]. Thus, a number of adults having CVD

events were not previously recommended for preventive treatment, whereas others are on treatment in spite of low CVD risk profiles.

An absolute risk approach that aims at individuals most likely to have events is more cost-effective because this approach tends to prevent more CVD events with a lower number of patients needed to treat [37, 38]. Compared to a risk factor counting model, an integrated risk model is advanced because it accounts for variability or intensity of risk factor levels and the progressive impact of age on total risk [39]. Generally, most CVD risk score models incorporate a group of traditional risk factors that include age, sex, smoking status, systolic BP, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and diabetes mellitus (DM). Some recent scores added a family history of CVD, ethnicity, deprivation score, and diagnosis of atrial fibrillation or rheumatoid arthritis into the models (Table 1.1).

Current guidelines for primary prevention of CVD [2, 5, 40, 41] are now mainly based on short-term absolute risk, the risk of having a CVD event in the next 5 to 10 years for the treatment decision. The most validated and widely used risk score are Framingham risk score (FRS) [42-44] and SCORE[45], however, these risk algorithms should be applied with caution because they were established using cohorts from the last decade with much higher CVD event rates, fewer preventive medications, less socioeconomically and ethnically diverse compared to current cohorts. The two most contemporary risk equations – QRISK 2[46] (2008) and the New Zealand Primary Prevention Equations (2018) [47] were developed from contemporary cohorts in the UK and New Zealand respectively, however they have not been comprehensively validated and calibrated in other regions. Most of the guidelines use 10-year CVD risk equations whereas the New Zealand and Australia guidelines adopt 5-year CVD risk equations [1, 2]. Compared to 10-year risk, the 5-year risk is likely to be more practical because most of the current evidence for preventive medications is from randomised controlled trials (RCT) of 5 years or less follow-up and prevention strategies might change within 10 years.

Considerations on absolute risk assessment

- Given that age is heavily weighted in the short-term absolute risk, such approach targets most of drug treatments to elderly populations. Thus, middle-aged individuals who have an extremely high value of a risk factor or significant comorbidities could have their risk underestimated and thus remain untreated (i.e. BP or lipid-lowering drug treatment). A new risk measure, a so-called 'lifetime' risk that estimates the incremental risk of having a CVD event during the rest of an individual's life has been recently recommended [48]. The JBS 3 guideline[49] used high lifetime risk as an indicator for BP lowering drug treatment in mildly elevated BP (e.g. systolic BP 140-159 and/or diastolic BP 90-99 mmHg). Due to scant evidence for the effectiveness and cost-effectiveness of applying this guideline, the 'lifetime' risk or 'heart age' should be considered for communicating risk and encouraging behaviour changes only [40, 50].
- Most risk algorithms are validated for adults under 75 years. CVD risk of the elderly at 75 years or over is estimated as 'minimal' risk. There is a concern about the decreased association between metabolic syndromes (e.g. obesity), systolic and/or diastolic BP with CVD risk and mortality, particularly in very old and/or frail and multimorbid, polypharmacy individuals [51-56].
- Some common conditions determine high-risk profiles: (1) renal dysfunction, CKD, (2) familial hypercholesterolemia, (3) DM accompanying with another RF (e.g. age). Other different conditions are specified in particular guidelines (Table 1.1).
- Individuals with absolute risk score near the threshold of treatment decision may be screened for preclinical vascular damage (coronary artery calcium, atherosclerotic plaques) or other factors that were not included in CVD risk algorithms (e.g. BMI, family history of premature CVD) to improve the risk predictors and decision making. In ESC and NICE guideline [40, 57], the authors noted concerns about conditions that may contribute to increasing CVD risk such as cardiotoxicity in cancer patients with chemotherapy or radiotherapy, autoimmune disease (e.g. rheumatoid arthritis, systemic lupus erythematosus).

Table 1.1. Absolute risk assessment for primary prevention of cardiovascular disease

Guidelines	Risk Score	Risk threshold (%)			Predicted outcomes	Risk factors	CVD risk equivalent (assumed to have high CVD risk)	Age range for screening
		Low	Moderate	High				
NVDPA[2] 2012, (Australia)	5-year Framingham risk [44]	<10	10-15	>15	'Hard' CHD + 'hard' CVE + angina, HF, PVD, TIA.	Sex-specific models. Traditional RFs + ECG-LVH	DM + age > 60 years, DM + microalbuminuria, moderate or severe CKD, SBP ≥180 and/or DBP ≥ 110 mmHg, TC> 7.5 mmol/L, TC/HDL-c ≥ 8, FH, Aboriginal and Torres Strait Islander adults > 74 years.	≥ 45 years, (Aboriginal and Torres Strait Islander peoples ≥ 35 years)
Australian NHF 2016 [58] (Australia)							(As above + diagnosis of TOD)	
New Zealand 2018 [1]	5-year New Zealand CVD risk [47]	<5	5-15	>15	'Hard' CHD + 'hard' CVE+ angina, HF, PVD, TIA	Sex-specific models. Traditional RFs+ ethnicity, deprivation score, family history of premature CVD, history of AF, BP- / lipid-	DM+ moderate CKD, severe CKD, FH, TOD	Men 45-74 yrs, women 55-74 years, (Maori, Pacific peoples or South-Asian peoples: men 30-74 years, women 40-74 years)

Guidelines	Risk Score	Risk threshold (%)			Predicted outcomes	Risk factors	CVD risk equivalent (assumed to have high CVD risk)	Age range for screening
		Low	Moderate	High				
						lowering medication, antithrombotic medication.		
ESC for CVD prevention 2016 [40], ESC for hypertension 2018 [59](Europe)	10-yr SCORE [45]	<1	1-4	≥ 5	Fatal CHD or fatal stroke.	Versions for use in high and low-risk countries. Traditional RFs *excluding* DM.	DM, moderate CKD, systolic BP ≥180 and/or diastolic BP ≥ 110 mmHg, TC > 8 mmol/L, FH.	Men 40-65 yrs, Women 50-65 years or post-menopausal
Canada guideline for hypertension 2018[3]	10-year Framingham risk	<15		≥ 15	'Hard' CHD + 'hard' CVE + angina, HF, PVD, TIA.	Sex-specific models. Traditional RFs+ BP-lowering medication,	DM, CKD, age ≥ 75	Age 45-75 years
Canada guideline for lipid management 2016[60]		<10	10-20	≥ 20			DM, CKD, FH, LDL-c ≥5 mmol/l.	
NICE for hypertensio	10-year QRISK2 [46]	<20		≥20		Traditional RFs+	DM, albuminuria, CKD, FH or other inherited disorder of	Adults 40-80 years

Guidelines	Risk Score	Risk threshold (%)			Predicted outcomes	Risk factors	CVD risk equivalent (assumed to have high CVD risk)	Age range for screening
		Low	Moderate	High				
n 2011 (UK) [5]					'Hard' CHD + 'hard' CVE + TIA.	treated hypertension, BMI, family history of premature CVD, deprivation score, ethnicity, rheumatoid arthritis, CKD, AF.	lipid metabolism, presence of TOD	
NICE for lipid management 2014 (UK)[57]		<10		≥10			Type 1 DM, albuminuria, CKD, FH or other inherited disorder of lipid metabolism, age ≥ 85	Adults 40-84 years
JBS 3 2014 (UK) [49]	10-year JBS3 risk calculator [49]	<10		≥10			DM+ age>40 years, moderate or severe CKD, FH, presence of TOD, significantly high lifetime risk, age ≥ 80.	Adults 40-74 years
SIGN149 2017 [61] (Scotland, UK)	10-year ASSIGN [62]	<20		≥20	CVD events are defined by ICD9 and 10 (fatal or non-fatal events of the circulatory system)	Sex-specific model. Traditional RFs + family history of premature CVD, rheumatoid arthritis, deprivation score.	DM+ age>40yrs, DM + age<40yrs+ albuminuria/duration of DM≥20 years / proliferative retinopathy/ autonomic neuropathy/ TOD, severe CKD, microalbuminuria, FH, TC > 8 mmol/L, SBP ≥160 and/or DBP ≥ 100 mmHg.	Adults 40-74 years (at any age for those with a family history of premature CVD or FH.

Guidelines	Risk Score	Risk threshold (%)			Predicted outcomes	Risk factors	CVD risk equivalent (assumed to have high CVD risk)	Age range for screening
		Low	Moderate	High				
ACC/AHA for hypertension 2017 (US)[63]	10-year Pooled Cohort Equations[64]	<10		≥ 10	'Hard' CHD + 'hard' CVE	Sex- and race-specific model. Traditional risk factors+ BP lowering medications.	DM, CKD, age ≥ 75	Adults 40-75 years
ACC/AHA for lipid management 2018 (US)[65]		<7.5	7.5-<20	≥20			DM, LDL-c ≥ 190 mg/dl	
USPSTF for lipid management 2016 (US)[66]		<7.5	7.5-10	>10			Not mentioned	

Abbreviations: ACC/AHA: American College of Cardiology/American Heart Association, AF: Atrial Fibrillation, CHD: Coronary Heart Disease, CVD: Cardiovascular disease, CVE: Cerebrovascular event, CKD: Chronic Kidney Disease, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, ESH/ESC: European Society of Cardiology, FH: Familial Hypercholesterolemia, HDL-c: High Density Lipoprotein cholesterol, HF: Heart failure, JBS: Joint British Societies, LDL-c: Low Density Lipoprotein cholesterol, LVH: Left Ventricular Hypertrophy, NHF: National Heart Foundation, NICE: National Institute for Health and Care Excellence, NVPDA: National Vascular Disease Prevention Alliance, PVD: Peripheral Vascular Disease, RF: Risk factor, SBP: Systolic blood pressure, SIGN: Scottish Intercollegiate Guidelines Network, TC: Total Cholesterol, TIA: Transient Ischemic attack, TOD: Target Organ Damage, USPSTF: US Preventive Services Task Force.

* 'Hard' CHD refers to myocardial infarction and fatal CHD, 'Hard' cerebrovascular disease refers to stroke and fatal stroke. Traditional risk factors refer to age, sex, smoking status, systolic BP, TC/HDL-c and DM.

BP lowering drug treatment in the primary prevention of CVD

In this thesis, BP lowering drug treatment is considered for primary prevention of CVD, thus management of complicated, resistant or secondary 'hypertension' is not covered. BP value throughout this thesis refers to clinic/office BP.

The effectiveness of BP lowering drug treatment

The effect of BP lowering drug treatment for CVD risk reduction has been well established in many RCTs [67, 68]. However, not all BP-lowering drugs are equal for CVD reduction. Alpha1-blockers, centrally acting antiadrenergic agents (a2-adrenoreceptor agonists and imidazoline receptor agonists), antialdosterone, and aliskiren effectively reduced BP, however, the benefits for CVD reduction, safety and tolerability of these agents have been unclear, thus these are only recommended as add-on therapies [69].

In contrast, at standard doses of the five most commonly-used of BP lowering drugs, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), dihydropyridine calcium channel blockers (CCB), β blockers and thiazides or thiazide-like diuretics (e.g. chlorthalidone) similarly reduce BP at a certain pre-treatment BP value. At higher pre-treatment BP value, therapeutic dose of BP lowering drug treatment produced a larger BP reduction [70]. As Law et al estimated, at an average pre-treatment BP of 154/97 mmHg, half or one standard dose of the five commonly-used BP lowering drugs reduced SBP by an average 7.1 mmHg and DBP by 9.1 mmHg over a 24 hours period [71]. Every 10 mmHg reduction of systolic BP was associated with a 20% reduction of CVD over 5 years irrespective of drug class, age or sex [1, 49, 70, 72]. The full effects of BP lowering drug regimens on CVD risk reduction were potentially achieved within one year [70, 73]. Different BP lowering drug classes have modest benefits in cause-specific CVD outcomes[40, 74] (Table 1.2), this difference in cause-specific outcomes may be attributable to small differences in BP reduction. The non-BP-related effect is also doubted, but no 'pleiotropic' effect has been identified [70, 75]. Noticeably, due to inferior effects on stroke prevention and adverse effects on metabolism syndrome (weight gain, lipid metabolism and new on-set DM), β blockers are no longer recommended as an

initial therapy. Due to additive efficacy of BP lowering drug classes and the likelihood of adverse effect at high dose, a combination of low dose drugs at initiation is preferable to titrating a single agent to high dose [71, 76].

Table 1.2. Effects of blood pressure lowering drug treatment on cause-specified outcomes and adverse effects.

	Inferior (-) /superior(+) effects on specific outcomes [40, 74]	**Compelling contraindications**	**Major adverse effects**	**Caution**
DHP-CCB	Stroke (+),heart failure (+)	NA	Peripheral vasodilation (peripheral oedema, flushing, headache, dizziness), postural hypotension, tachycardia, palpitations, chest pain, gingival hyperplasia	NA
TZ	Heart failure (++)	Gout	Lipid metabolism, new on-set DM, sudden death with high dose (4x standard dose), postural hypotension, dizziness, hypokalemia, hyponatraemia, hyperuricemia, hyperglycaemia	'Triple whammy' (ACEI/ARB +diuretic +NSAID) can cause acute kidney injury
ACEI	LVH (+), microalbuminuria (+), renal function (+).	Pregnancy, bilateral renal artery stenosis, hyperkalaemia	Dry cough, hyperkalaemia, renal impairment, angioedema	
ARB			Hyperkalaemia, renal impairment	

Abbreviation: ACE-I: Angiotensin Converting Enzyme Inhibitors, ARB: Angiotensin II Receptor Blockers, DHP-CCB: Dihydropyridine Calcium Channel Blocker, DM: Diabetes Mellitus, LVH: Left Ventricular Hypertrophy, NA: Not Applicable, NSAID: Nonsteroidal anti-inflammatory drugs, TZ: Thiazide or thiazide-like diuretics.

When to initiate a BP-lowering drug?

Historically, BP thresholds for drug treatment initiation heavily focussed on diastolic BP until the performance of Systolic Hypertension in the Elderly Program (SHEP) trials in the 1990s. Since then the focus was shifted to systolic BP (Figure 1.3) [77]. In a large study with 1.25 million participants aged 30 years or older, Rapsomaniki et al[56] showed that systolic and diastolic BP were

differently associated with different types of CVD events. Systolic BP had a stronger association with stroke, CHD and CVD events whereas diastolic BP had a stronger association with abdominal aortic aneurysms.

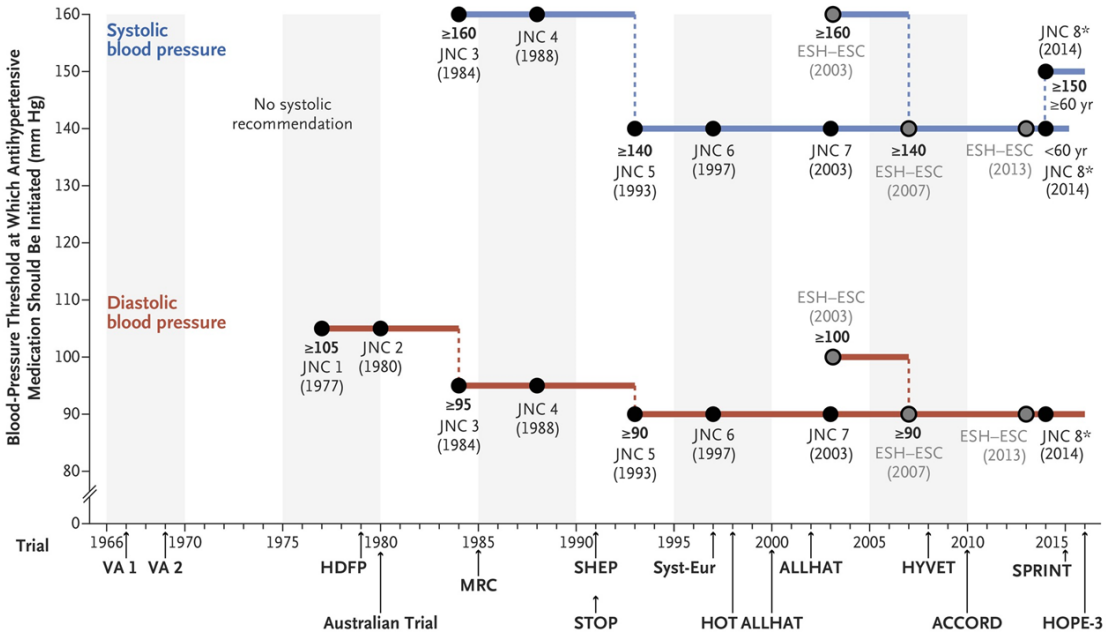


Figure 1.3 Blood pressure thresholds for drug treatment initiation.

Figure adapted from Pfeffer et al. New England Journal of Medicine. 2016; 375(18):1756-1766[77].

In the past couple of years there have been significant changes to the BP thresholds for drug treatment initiation down to as low as 120-130 mmHg of systolic BP. Later trials and observational studies demonstrated a continuous, log-linear relationship between risk of CVD and BP even at a modest value of 115/75 mmHg [78, 79]. Any commonly-used BP-lowering drug classes induce similar relative CVD risk reduction at any baseline BP threshold [70, 74], age[80], sex[81], diagnosis of DM[82], CKD[83] or not, and any baseline CVD risk [84] however, absolute risk reduction is greater in participants at higher baseline CVD risk [84, 85]. Thus, a risk approach is more beneficial and cost-effective than a BP-threshold approach (e.g. BP ≥ 140/90 mmHg) that could undertreat those with high risk [84, 86, 87]. Still, JNC 8 (2014) in the US heavily depends on age and BP thresholds[41]. As short-term absolute risks overweighted age in their calculations, young or middle age individuals with significantly elevated BP (e.g. BP ≥160/100 mmHg) tends to be underestimated as 'low-moderate' risk and remain untreated [86]. In addition, most of the absolute risk algorithms account

for systolic BP only, thus, an absolute risk approach in conjunction with BP threshold is recommended.

Current guidelines for BP lowering drug treatment (Table 1.3)

High-risk settings

In terms of the primary prevention of CVD, high-risk settings refer to individuals whose absolute risk exceed a threshold or those with the presence of CVD risk equivalents indicated by each guideline (Table 1.1). General recommendations for the high-risk population are substantially based on evidence that recommends an early initiation of pharmacotherapy [70, 74, 84, 88-93] because the benefits of BP lowering drug treatment were recorded from a systolic BP of 130 mmHg or higher [92, 93].

Guidelines in the UK [5, 49, 61] and Europe[40] recommend a BP threshold of 140/90 mmHg, whereas Australian[2, 58] guidelines prompt an immediate treatment regardless of BP levels. The recent SPRINT trial showed that lowering systolic BP below 120 mmHg provided little further benefits in spite of no increased risk of CVD or mortality [90, 94, 95]. Others are concerned about serious adverse events of intensive pharmacotherapy including hypotension, syncope, electrolyte abnormalities, acute kidney injury, or acute renal failure. Recently guidelines from Canada (2018), New Zealand (2018) and ACC/AHA US (2017) have a BP threshold of 130/80 mmHg at which efficacy and safety are likely to be balanced [1, 3, 63, 94, 96].

Low-moderate risk settings

In general, most guidelines [1-3, 5, 49, 58, 61] consider that a persistent BP of 160/100 mmHg is sufficiently high to establish a BP lowering drug treatment. In the HOPE-3 trial [97] pre-specified for intermediate risk population, no significant effect of BP lowering drug treatment was recorded, however substantial CVD reduction was observed in those whose BPs were higher than 143 mmHg. In a secondary analysis of HOPE-3 trial, Dagenais et al showed that such substantial benefits disappeared in participants with healthy lifestyles[98]. Thus, healthy lifestyle tended to sufficiently reduce CVD risk in an intermediate CVD risk setting, and benefits of BP lowering drug treatment in a low-moderate setting remains unclear, particularly in those with BP ranging from 140 to 159

mmHg. However, the US and European guidelines[40, 63] persist with the traditional threshold of 140 mmHg of systolic BP.

Table 1.3. Blood pressure thresholds to initiate blood pressure drug treatment according to absolute CVD risk stratification.

Guidelines	Low risk	Moderate risk	High risk/CVD risk equivalent
Australian hypertension 2016 (Australia) [58]	160/100	140/90	Any blood pressure level
Canada guideline for hypertension 2018 (Canada) [3]	160/100 (no risk factors)	140/90	SBP ≥ 130 irrespective of DBP
			130/80 for DM
NVDPA guideline for CVD prevention 2012 (Australia) [2]	160/100		Any blood pressure level [70, 82]
New Zealand guideline 2018 [1]	160/100		130/80
SIGN 2017 [61] (Scotland)	160/100		Any blood pressure level for DM, severe CKD, albuminuria, dialysis[99, 100]
			140/90 [70, 83-85, 89, 91, 99-101]
NICE for hypertension 2011[5], JBS3 2014[49] (UK)	160/100		140/90 [70]
ACC/AHA hypertension 2017 [63] (US)	140/90 [79, 88, 102-104]		130/80 [70, 74, 84, 88-92]
ESC/ESH for CVD prevention 2016 [40], ESC/ESH for hypertension 2018 [59] (Europe)	140/90		

Abbreviation: ACC/AHA: American College of Cardiology/American Heart Association, CKD: Chronic Kidney Disease, CVD: Cardiovascular disease, DM: Diabetes Mellitus, ESC: European Society of Cardiology, JBS: Joint British Societies, NICE: National Institute for Health and Care Excellence, NVPDA: National Vascular Disease Prevention Alliance, SIGN: Scottish Intercollegiate Guidelines Network

The effectiveness of BP lowering drug treatment in mildly elevated BP

Two systematic reviews [88, 105] specifically focused on mildly elevated BP (SBP 140-159 mmHg and/or DBP 90-99 mmHg) have been conducted. (1) In a systematic review by Diao et al [105], no significant benefits for CVD or mortality were observed. The review was restricted to RCTs with the control group of placebo or untreated. Only four studies (MRC, SHEP, VA-NHLBI and ANBP) of 8912 participants were included with a maximum follow-up of five years. A small number of CVD events were recorded in these trials, indicating the low-risk profile of the participants. The review by Diao et al included the SHEP trial that required participants to have systolic BP exceeding 160 mmHg and a diastolic BP lower than 90 mmHg, though only 7 out of 4736 SHEP participants were included in this review. (2) In a larger systematic review of 11 RCTs (15266 participants) by BPLTTC 2015 [88], a significant reduction of major CVD events, CVD and all-cause mortality was observed in the active or intensive treatment group. However, the BPLTTC review included RCTs with the continuation of previous BP lowering drug treatment (ADVANCE, Diabhycar, PART-2, BENEDICT and SCAT), thus baseline BP values were likely to be underestimated and misclassified as 'mild hypertension'. In Table 1.4, only RCTs with discontinuation of previous treatment were pooled and the treatment effects were also standardised to 10 mmHg reduction of systolic BP. The effect on CVD and total death outcomes were no longer significant, however, the effect on stroke remained significant with OR 0.21 (0.07-0.64). However, the significant effects on stroke were exclusively observed in RCTs with 100% diabetic participants (ABCD and UKPDS), they were more likely to be at increased CVD risk. In a retrospective longitudinal cohort study[106] on low risk participants (QRISK2<20%) with mild hypertension, no significant reduction on major CVD events or mortality were observed in treated participants, this group were more likely to have higher risk of adverse events such as hypotension, syncope, bradycardia, electrolyte abnormalities, falls and acute kidney injury. In contrast, a recent stratified meta-analysis by Brunström et al[107] found a significant reduction of major CVD events with a RR 0.88 (0.80-0.96) in a group of primary preventive trials with mean SBP ranging from 140-159 mmHg, yet these trials included at least 50% of participants with previous CVD.

Table 1.4. Summary of effects of BP lowering drug treatment in mildly elevated BP [88]

Characteristics	ANBP	MRC	VA-NHLBI	PREVEND	ABCD (H)	ABCD (N)	UKPDS	Overall effects
Comparison	Chlorothiazide vs placebo	Bendrofluazide /propranolol vs placebo	Chlorthalidone + reserpine vs placebo	Enalapril vs placebo	More vs less intensive; nisoldipine or enalapril		More vs less intensive; captopril or atenolol	NA
No of participants/original trials	1832/3427	6061/17354	1012/1012	212/864	213/470	143/480	453/1148	NA
Mean/median follow-up (years)	4	5	4.5	3.9	5.0	5.1	8.3	NA
Mean BP mmHg	NA	NA	NA	147/84	144/94	147/85	145/94	NA
Previous BP lowering drug treatment (%)	0	0	0	0	37 (stopped)	36 (stopped)	0	NA
% DM	0	0	0	5	100	100	100	NA

Characteristics	ANBP	MRC	VA-NHLBI	PREVEND	ABCD (H)	ABCD (N)	UKPDS	Overall effects
SBP reduction mmHg	NA	NA	NA	7.2	8.7	7.1	9.1	NA
Outcomes RR								
CVD events	NA	0.93 (0.68-1.2)	1.60 (0.52-4.91)	0.43 (0.12-1.46)	0.45 (0.20-1.02)	1.33 (0.55-3.23)	NA	0.88 (0.68-1.15)
Standardised	NA	NA	NA	0.30 (0.06-1.68)	0.40 (0.16-1.03)	1.49 (0.43-5.21)	NA	0.57 (0.29-1.14)
CHD event	NA	1.08 (0.76-1.55)	1.60 (0.52-4.91)	NA	1.10 (0.38-3.14)	2.23 (0.55-9.00)	0.98 (0.53-1.81)	1.12 (0.85-1.49)
Standardised	NA	NA	NA	NA	1.12 (0.33-3.74)	3.10 (0.43-22.07)	0.98 (0.50-1.92)	1.11 (0.63-1.94)
Stroke	NA	0.50 (0.24-1.08)	NA	0.08 (0.00-1.57)	0.46 (0.11-1.90)	0.22 (0.02-1.98)	**0.21 (0.07-0.64)**	**0.34 (0.20-0.59)**
Standardised	NA	NA	NA	0.03	0.41	0.12	**0.18**	**0.21**

Characteristics	ANBP	MRC	VA-NHLBI	PREVEND	ABCD (H)	ABCD (N)	UKPDS	Overall effects
				(0.00-1.62)	(0.08-2.07)	(0.01-2.61)	**(0.06-0.61)**	**(0.08-0.51)**
CVD death	NA	NA	NA	1.80 (0.16-20.16)	**0.11 (0.01-0.90)**	2.36 (0.44-12.57)	NA	0.66 (0.26-1.68)
Standardised	NA	NA	NA	2.26 (0.08-64.82)	0.08 (0.01-0.89)	3.35 (0.32-35.36)	NA	0.72 (0.16-3.25)
Total death*	1.20 (0.58-2.46)	0.76 (0.54-1.07)	7.35 (0.46-117.60)	0.89 (0.28-2.84)	**0.30 (0.11-0.81)**	1.62 (0.47-5.53)	0.81 (0.44-1.49)	0.81 (0.63-1.04)
Standardised	NA	NA	NA	0.85 (0.17-4.27)	0.22 (0.06-0.83)	2.02 (0.34-12.16)	0.79 (0.41-1.53)	0.71 (0.42-1.20)

Abbreviation: ABCD: Appropriate Blood pressure Control in Diabetes trial, ANBP: Australian National Blood Pressure study, BP: blood pressure, MRC: Medical Research Council trial, PREVEND-IT: Prevention of Renal and Vascular End stage Disease Intervention Trial, RR: Risk Ratio, SBP: Systolic blood pressure, UKPDS: UK Prospective Diabetes Study, VA-NHLBI: Veterans Administration-National Heart, Lung, and Blood Institute trial.

Overall and standardised effects are recalculated from data provided in the 2015 BPLTTC review[88]. RCTs with the continuation of previous treatment were excluded due to BP underestimation. ¶ Standardised to a 10 mmHg reduction of systolic BP that is calculated by multiplying the log OR (and its standard error) by 10/average SBP reduction. Bold: statistically significant outcome. *: Used Peto OR due to 0 events in a controlled group of VA-NHLBI.

Concerns about irreversible damage if BP lowering drug treatment is delayed

As reported by Wilkins et al[108], an individual with optimal risk profiles could delay CVD events by 8-14 years compared to those with at least two major risk factors. Concern is around the high residual risk (after-treatment risk) despite intensive drug treatments or irreversible damage if reserving treatment to high-risk individuals only [85, 109-111]. Thomopoulos et al [85] reported that 'residual' risk was higher in high-risk settings, in other words, treatment in high-risk profiles was more likely to fail. However, baseline CVD risks estimation in the Thomopoulos et al analysis was based on actual incidence death rates of CVD in controlled groups. Noticeably, the controlled groups were either placebo, no treatment or less intensive treatment regardless of whether previous BP lowering drug treatment was continued or not, thus the calculated CVD risk tended to be underestimated and patients misclassified. Besides, assessment of 'residual risk' is impacted by other concomitant preventive therapies (e.g. lifestyle modifications, lipid-lowering or antiplatelet treatment), drug adherence, achieved BP or visit-to-visit BP variation [112, 113].

In the paucity of evidence of short-term benefits or harms, the concern of BP lowering drug treatment in those with low-risk has been shifted to long-term effects. As most of the RCTs were mainly followed-up to a maximum of 5 years, after the end of the in-trial phase, some trials were extended. In the extended phase, all participants returned to usual care and were advised to receive active therapies. Outcomes were obtained by health records or national death index linkages. In Table 1.5, to minimize the impact of carry-over effects of previous treatments, some placebo-controlled RCTs without previous treatment or RCTs with wash-out previous treatment were reviewed to estimate the effect of treated versus untreated group[114-123]. In relatively low-risk RCTs (Oslo, PREVEND-IT), the 5-year follow-up phase observed a significantly low cerebrovascular event rate in the active treatment group compared to the placebo group. However, the beneficial effects disappeared in the long-term phase of both trials, noticeably, the 5-year and 10-year Oslo trial recorded a higher number of fatal CHD events in the active group compared to the placebo group but this was not statistically significant; in the 40-year Oslo trial the harm of active treatment on fatal CHD became significant HR 1.51 (1.01-2.26).

Participants in the Oslo trial were treated with a high dose of thiazide diuretic that is not recommended in current practice. As a high dose of a thiazide diuretic is highly relevant to a high risk of new onset diabetes mellitus (DM), DM with long duration may lead to increase CHD risk. In contrast, the SHEP and Syst-Eur trial recorded a sustained reduction of CVD mortality in the active treatment group in both the short- and long-term phases. All participants in these trials tended to be at increased baseline CVD risk when inclusion criteria restricted to the elderly with highly elevated BP (systolic BP ≥ 160 mmHg). Most of the post-trial observational studies have a common limitation that information of post-trial treatment was not sufficiently recorded, however as a nature of randomisation, it is unlikely that the treatment regimens were uneven or more pronounced between the originally randomised groups. Generally, the concern about the long-term effects of BP lowering drug treatment in a low-risk setting with mildly elevated BP remained questionable.

Table 1.5. Summary of short- and long-term effects of blood pressure lowering drug treatment for primary prevention of cardiovascular disease

Characteristics	Oslo[114-116]	PREVEND-IT [117, 118]	SHEP [119-121]	Syst-Eur [122, 123]
Comparison	Hydrochlorothiazide 50 mg vs placebo	Fosinopril 20 mg vs placebo	Chlorthalidone 12.5 mg vs placebo	Nitrendipine 10 mg vs placebo
% Active treatment in post-trial phase	80 (both groups)	Reported equal	NA	75 (both groups)
Mean age years	45	51	72	70
Mean BP mmHg	156/97	127/74	170/76	174/85
CVD history (%)	0	3	5% MI, 1.5% stroke	30
DM (%)	0	3	10	10
SBP reduction mmHg in-trial phase	17	1	11	11
'Ethical' roof to initiate treatment in placebo (mmHg)	180/110	NA	240/115 (single visit) Sustained 220/90	SBP 219
Outcomes	A: 407, P: 379	A:431, P:433	A:2365, P:2371	A:2398, P:2297
	5-yr (1972-1977)	**5-yr (1998 - 2003)**	**5-yr (1985 - 1990)**	**2-yr (1995 - 1997)**
	+CVE: 0 (A), 7 (P)	+Nonfatal CVE: 1 (A), 10 (P)	+CVE: RR 0.73 (0.57-0.94)	+Stroke: RR 0.61 (0.44-0.87)
	+CHD: 20(A), 13 (P), NS.			

Characteristics	Oslo[114-116]	PREVEND-IT [117, 118]	SHEP [119-121]	Syst-Eur [122, 123]
	+Fatal CHD: 6(A), 2 (P), NS +Total deaths: NS	+Nonfatal: MI, HF, and PVD: NS. + Fatal: CVD, total: NS	+CHD: 0.75 (0.60-0.94) +CVD: 0.68 (0.58-0.79) +Fatal: stroke, CVD, total: NS	+CVD: RR 0.74 (0.60-0.91) + MI, HF:NS +Fatal: CVD, cancer, total: NS
	10-yr (1972-1982) +Fatal CHD: 14 (A), 3 (P), NS +Total deaths: NS 40-yr (1972-2011) + Fatal MI: HR 1.51 (1.01-2.26) +Fatal: CVE, total: NS	**9.5-yr (1998-2008)** + Nonfatal: MI, HF, PVD, CVE, CVD: NS. + Fatal: CVD, total: NS.	**14-yr (1985-2000)** +Fatal CVD: HR: 0.86 (0.76-0.97) + Fatal: stroke, non-CVD, total: NS 22-yr (1985-2006) +Fatal CVD: 0.89 (0.80-0.99) +Fatal: CHD, stroke, total: NS	**6-yr (1995-2001)** +Stroke: RR 0.73 (0.57-0.93) +CVD: RR 0.87 (0.76-0.99) + MI, HF:NS +Fatal: CVD, cancer, total: NS

Abbreviation: A: Active, CHD: Coronary Heart Disease, CVD: Cardiovascular disease, CVE: Cerebrovascular event, DM: Diabetes Mellitus, HF: Heart failure, MI: Myocardial Infarction, NS: Not statistically significant, P: Placebo, PREVEND-IT: Prevention of Renal and Vascular End-stage Disease Intervention Trial, RR: Risk Ratio, SBP: Systolic blood pressure, SHEP: Systolic Hypertension in the Elderly Program trial, SYST-Eur: Systolic Hypertension in Europe Trial

Lipid-lowering drug treatment (LLT) in primary prevention of CVD

In this thesis, lipid-lowering drug treatment (LLT) is considered for the purpose of primary prevention of CVD, thus management of complicated or secondary 'dyslipidaemia' is not mentioned.

Lipid profiles include total cholesterol, HDL-c, LDL-c and triglyceride (TG). LDL-c is calculated by the Friedewald equation given that the ratio of total cholesterol and triglyceride is constant[124]. When TG exceeds 4.5 mmol/L or fasting tests are not available, non-HDL-c that is calculated by total cholesterol minus HDL-c obtained from a non-fasting test may be eligible for treatment decision. Despite HDL-c being strongly associated with CVD risk, treatment primarily aimed at improving HDL-c contributes modest effects to CVD reduction[125, 126]. In contrast, statins that primarily reduce LDL-c are associated with substantial major CVD reduction, thus are recommended as the first line therapy[127].

Statin

Different statins produced different magnitudes of LDL-c reduction at a certain dose, atorvastatin and rosuvastatin have higher lipid-lowering efficacy, and thus they are considered high potency statins (Table 1.6). Higher doses of statins are log-linearly associated with a larger LDL-c reduction, each doubling of the dose of statins obtains approximately a further 6% LDL-c reduction irrespective of pre-treatment LDL-c value [128]. Based on the percentage of achieved LDL-c reduction, statins are classified as low, moderate and high intensity with LDL-c reduction of less than 30%, 30-40% and more than 40% respectively [57].

Table 1.6. Statin doses and effects on LDL-c reduction [128]

Daily dose (mg)						Notes
Statin	5	10	20	40	80	
Fluvastatin	10%	15%	21%	27%	33%	Metabolised by cytochrome P450 2C9-> cautious with drug interaction[129]
Pravastatin	15%	20%	24%	29%	33%	
Lovastatin	-	21%	29%	37%	45%	Metabolised by cytochrome P450 3A4 -> interact with potent cytochrome P450 3A4 inhibitors, even grapefruit.[129] + Simvastatin 80 mg may be harmful (greater risk of myopathy) [130] + High dose of atorvastatin increased liver enzyme level (reversible)[131]
Simvastatin	23%	27%	32%	37%	42%	
Atorvastatin	31%	37%	43%	49%	55%	
Rosuvastatin	38%	43%	48%	53%	58%	

Low intensity Moderate intensity High intensity

Given that any statins at any doses effectively reduced major CVD risk, every 1 mmol/L reduction of LDL-c was associated with 25% reduction of major CVD events during each year irrespective of pre-treatment LDL-c or baseline CVD risk [130], although greater CVD risk populations obtained greater absolute risk reduction [127, 132, 133]. The benefits of statins accumulate over years, longer treatments obtained larger absolute risk reduction [134]. Thus, current guidelines encourage early initiation of moderate-high intensity statins in high CVD risk individuals at any level or at mildly elevated LDL-c [1, 2, 135] (Table 1.7). As adverse effects of statin are dose-dependent, a low-moderate dose of high potency statins is preferable.

Table 1.7 Initiation of statins based on absolute cardiovascular disease risk and serum cholesterol thresholds

Guidelines	Low risk	Moderate risk	High risk /CVD risk equivalent
Canada guideline for lipid management 2016 [60]	LDL-c ≥ 5 mmol/L	LDL-c ≥ 3.5 or Non-HDL-c ≥ 4.3 or ApoB ≥ 1.2 g/l	Any serum cholesterol level
ESC 2016 (EU)[40]	LDL-c≥ 4.9 mmol/L	LDL-c≥ 2.6 mmol/L	**SCORE 5-9:* LDL-c≥ 1.8 mmol/L *SCORE ≥ 10 Any LDL-c level
SIGN 2017 (Scotland)	TC > 8 mmol/L		Any serum cholesterol level
NVDPA (2012) [2]	TC>7.5 mmol/L or TC/HDLc ≥ 8		Any serum cholesterol level
New Zealand 2018[1]	TC/HDLc ≥ 8		Any serum cholesterol level

Guidelines	Low risk	Moderate risk	High risk /CVD risk equivalent
NICE for cholesterol management 2014[57], JBS3 2014 (UK)[49]	Not recommended		Any serum cholesterol level
USPTS for lipid management 2016 (US) [66]	Not recommended		Additional RFs (smoking, hypertension, DM, dyslipidaemia)
ACC/AHA for lipid management 2018 (US)[65]	LDL-c>4.9 mmol/L LDL-c>1.8 mmol/L in DM.	LDL-c ≥ 4.1 or Additional RFs	LDL-c > 1.8 mmol/L

Abbreviations: ACC/AHA: American College of Cardiology/American Heart Association, DM: Diabetes Mellitus, ESC: European Society of Cardiology, HDL-c: High Density Lipoprotein cholesterol, JBS: Joint British Societies, LDL-c: Low Density Lipoprotein cholesterol, NICE: National Institute for Health and Care Excellence, NVPDA: National Vascular Disease Prevention Alliance, SIGN: Scottish Intercollegiate Guidelines Network, USPSTF: US Preventive Services Task Force

Adverse effects of statins

Statin use is associated with myopathy, new-onset diabetes, elevated liver enzyme levels and haemorrhagic stroke. Statins at higher doses are associated with increased risk of adverse effects, noticeably simvastatin 80 mg was significantly associated with increased risk of myopathy[130]. Besides, most statins are metabolised through cytochrome P450 system (except pravastatin and rosuvastatin), thus they are more likely to have drug interactions. Simvastatin and atorvastatin are metabolised via cytochrome P450 3A4, concomitant use of cytochrome P450 3A4 inhibitor agents (e.g. 'azole' anti-fungal agents, amiodarone, verapamil, diltiazem) or a less potent inhibitor such as grapefruit juice increases the plasma level of these statins and subsequently enhances the risk of adverse effects[129]. At a moderate-high dose of statins, incidence rates of statin-related adverse effects are very low, in other words, the evident benefits on CVD outcomes substantially exceed potential harms of statin. As estimated by Collin et al[134], treating 2000 healthy individuals with a statin would prevent 200 major CVD events and would cause one case of myopathy, one to two cases of haemorrhagic stroke and one to two cases of new-onset DM.

Non-statin agents

Other lipid-lowering agents including fibrates[136-139], bile acid sequestrant [140], ezetimibe[141, 142] have modest effects on LDL-c or TC, inconsistent impacts on CVD outcomes and have higher adverse effects, thus they are not routinely recommended as monotherapy for the primary prevention of CVD (Table 1.8) [135]. Lack of evidence for the benefit of combinations of these drugs with statins has been found except for a combination of ezetimibe with simvastatin that yielded a substantial CVD risk reduction in people with advanced chronic kidney disease[143], still titrating statins to the maximum tolerated dose is preferable. A combination with non-statin agents is reserved for a very high-risk setting (e.g. familial hypercholesterolemia) or those accompanying significant disorders of HDL-c or TG. Nicotinic acid (niacin) [144, 145] has no clear evident benefits on CVD outcome and potentially increases overall mortality, thus it is no longer recommended as a preventive therapy. A new LLT agent, proprotein

convertase subtilisin/kexin type 9 (PCSK9) was associated with a substantial LDL-c and MI reduction, however, the evidence base is a small number of studies with short-term follow-up[146, 147]. Thus PCSK9 has not been widely recommended or used to date.

Table 1.8. Summary effects of non-statin agents.

Non-statin agents	Beneficial effects on serum cholesterol	Beneficial effects on CVD outcomes	Major adverse effects	Indications
Fibrate (except gemfibrozil)	↙↙ TG, ↙LDL-c, ↗HDL-c	↙CVD[148]	↗ Serum creatinine (reversible) [148]	Not tolerated/ contraindicated statins ± marked elevated TG, low HDL-c
Bile acid sequestrants	↙LDL-c	↙CHD[149]	↗ TG, GI irritation, constipation. [149]	FH, not tolerated/ contraindicated statins.
Ezetimibe	↙LDL-c	Unclear (no study on primary prevention)	↗ Liver enzyme, myopathy[150]	
PCSK9 inhibitors	↙↙LDL-c, ↗HDL-c	↙MI (mixed with secondary prevention)[146]	Potential neurocognitive dysfunction (mixed with secondary prevention)[147]	Not tolerated to statins and other non-statin agents
Nicotinic acid (niacin)	↗↗HDL-c, ↙TG, ↙LDL-c	No benefits (even for secondary prevention)[144]	Harmful effects on GI bleeding and infection, potentially ↗ all-cause mortality[144, 145]	Not recommended

Abbreviation: CVD: Cardiovascular disease, GI: Gastrointestinal, HDL-c: High-Density Lipoprotein cholesterol, LDL-c: Low-Density Lipoprotein cholesterol, MI: Myocardial Infarction, TG: Triglyceride, FH: Familial Hypercholesterolemia.

Lipid-lowering drug treatment in the elderly

Current guidelines recommend LLT (e.g. statins) following the absolute CVD risk approach for the elderly aged 65 years or over (Table 1.7). As most

of the CVD risk algorithms are heavily weighted for age, the elderly are more likely to have a high CVD risk prediction, even if they have otherwise optimal risk profiles. Thus, most of them are eligible for LLT, however evidence for their benefits is attributable from RCTs mixed with secondary prevention[151] or with younger age settings[152]. In the elderly subgroup analysis incorporated in the meta-analysis by Brugts et al[153], no significant effects on major CHD, cerebrovascular events or all-cause mortality were recorded, although the authors did not report the specific outcomes of MI or stroke. It is doubtful that the effects on cerebrovascular events could be diminished by the adverse effects of statins on haemorrhage stroke. In a meta-analysis[154] restricted to RCTs or subgroups of primary prevention in the elderly aged 65 years or over a significant reduction in MI RR 0.61 (0.63-0.93) and stroke RR 0.76 (0.63-0.93) was observed, however, no survival benefits were accrued. As the included RCTs were followed up less than 5 years and some of the included studies (ASCOT-LLA[155], CARDS[156] and JUPITER[152]) terminated earlier than planned, the effects on MI and stroke may be overestimated and mortality outcomes may require longer observations. In a recent meta-analysis[157] of the elderly subgroups from JUPITER and HOPE-3 trial, rosuvastatin substantially reduced CVD with HR 0.51 (0.38-0.69) in subgroup aged 65 to younger than 70 years, HR 0.74 (0.61-0.91) in subgroup aged 70 years or over, still, no mortality outcomes were reported. Some RCTs were extended after study termination for long-term follow-up of mortality outcome, only two extended RCTs have a large number of elderly participants indicated by mean age at 65 years or over (Table 1.9). As presented in Table 1.9, no trials observed substantial effects on mortality outcomes both in-trial and post-trial phases, however both ALLHAT-LLT and PROSPER trial included more than 40% of secondary prevention subsets. Mortality effects of statins or LLT for primary prevention of CVD in the elderly remained unclear. STAREE is an ongoing RCT that will inform us of the benefits and harms of statins in the elderly over 70s.

Table 1.9. Summary of effects of statins on the elderly

Characteristics	ALLHAT-LLT[158, 159]	PROSPER [151, 160]
Comparison	Pravastatin 40 mg vs usual care	Pravastatin 40 mg vs placebo
% Active treatment in post-trial phase	Not reported	Not reported
Mean age yrs	66	75
Mean LDL-c mmol/L	3.8	3.8
Age ≥ 65 yrs (%)	56.1	100
CVD history (%)	44.7	43.2
DM (%)	39.3	11
LDL-c reduction mmol/L in-trial phase	0.4	1.3
Outcomes	**6-year phase (1994-2002)** +Combined CHD/ stroke, heart failure, cancer: NS +All-cause/CVD mortality: NS.	**3-year phase (1997-2002)** +Combined CVD HR 0.85 (0.75-0.97), CHD HR 0.81 (0.69-0.94). +CHD death HR 0.76 (0.58-0.99) +Stroke, heart failure, cancer: NS +All-cause/CVD mortality: NS.
	10-year phase (1994-2006) +Combined CVD/CHD/ stroke, heart failure: NS +All-cause/CVD mortality: NS.	**9-year phase (1997-2009)** +Combined CHD HR 0.81 (0.69-0.95). +Combined CVD, stroke, cancer: NS +All-cause/CVD mortality: NS.

Abbreviations: ALLHAT-LLT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial, CHD: Coronary Heart Disease, DM: Diabetes Mellitus, HR: Hazard Ratio, LDL-c: Low Density Lipoprotein cholesterol, MI: Myocardial Infarction, NS: Not statistically significant, PROSPER: Pravastatin in elderly individuals at risk of vascular disease trial, TG: Triglyceride

Aims and sources of data used in this thesis

This thesis contributes to filling in the gaps around the effectiveness of BP and LLT for primary prevention of CVD according to absolute CVD risk. However, the research focuses on settings with low absolute CVD risk and

mildly elevated BP for BP lowering drug treatment and the elderly for lipid-lowering drug treatment. Four studies incorporated in this thesis aim to:

- Assess which group of individuals classified by absolute risk benefits from actively BP lowering drug treatment versus placebo for CVD events. (Chapter 2)

Chapter 2 presents a post-hoc subgroup analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons. ANBP is a community-based placebo-randomised controlled trial in 3244 participants aged 35 to 69 years. ANBP was conducted between 1973 and 1979 and was selected because it was placebo-controlled and patients in the control arm of the study would not have been taking a BP lowering medication previously unless they had very high levels of BP. Thus, the effect of treated vs untreated or delayed BP lowering drug treatment according to absolute CVD risk could be assessed.

All analyses were based on the modified 'intention to treat' principle. Treatment effects were assessed by hazard ratio (HR), absolute risk reduction (ARR) and number needed to treat (NNT). In a subgroup analysis, participants were stratified by tertile of the 5-year Framingham absolute risk score with low (<6%), moderate (6% -17%) and high risk (>17%). Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the Hazard ratio and a Cochran's Q test for the absolute risk reduction.

Although the study in the ANBP maintained the randomisation, the subgroup analysis by absolute CVD risk would reduce the study power due to the reduced sample size in each subgroup. As multiple statistical tests were performed, the results should be interpreted carefully due to the risk of false-positive results.

- Investigate the short- and long-term effects of BP lowering therapy on those with elevated BP over a spectrum of absolute risk on all-cause and disease-specific mortality.

Chapter 3 presents a post-hoc observational study of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT is a comparative RCT of three treatment arms (diuretic, CCB, ACE-I). 33,357 ALLHAT participants were recruited in 623 centres in the USA, Canada, Puerto Rico and the US Virgin Islands. In the current study, the participants would be reclassified to previous treatment and treatment naïve group based on their treatment status before enrolling in the ALLHAT trial. ALLHAT was selected due to its large sample size and extended follow-up including post-trial phase up to 17 years.

A Cox proportional hazard model was used to estimate the effects of BP treatment naive on mortality outcomes. Treatment effects were adjusted for baseline and in-trial characteristics. Also, a subgroup analysis by estimated 10-year Framingham risk score (FRS) was performed to stratify participants into low (<20%), moderate (20-30%) and high risk (>30%) group. In the subgroup analysis by absolute CVD risk, interaction among CVD subgroup was tested by a baseline treatment status x absolute CVD risk stratification term in Cox models.

This study would be biased by 'confounding by indication'. Participants in previous treatment were more likely to be at higher underlying CVD risk (e.g. subclinical vascular damages or family history of CVD) or they were exposed to uncontrolled BP with lifestyle modifications. Thus, the mortality rate in these participants were expected to be higher than 'treatment naïve' participants. This issue should be put into consideration when interpreting the results. There are several methods to handle the confounding by indication such as propensity score, instrumental variable and multivariate adjusted models. Adjustment model was chosen because we wanted to present results from models with progressively larger sets of covariates, since there was not consensus about where some variables were on the causal pathway, and results with and without adjustment of such variables would be valuable.

- Investigate short- and long-term effects of BP lowering pharmacotherapy in middle-aged individuals with mildly elevated BP stratified by absolute

risk for primary prevention of CVD with a particular focus on the low risk (<10% absolute risk over 5 years) group: a systematic review and meta-analysis.

Chapter 4 presents a systematic review meta-analysis of ~~RCTs~~ post-trial studies in middle-aged individuals with mildly elevated BP. We compared the effects of delayed BP treatment (placebo/untreated during the trial or no previous treatment at trial entry) versus early treatment (actively treated during the trial or previous BP treatment at trial entry) on mortality in the short-term (5-year in-trial period) and long-term (≥10 years in total period). The data were pooled using Peto odds ratio . A subgroup analysis by 10-year Framingham risk score was performed. Vigorous efforts in accessing individual data was put in to identify eligible participants.

- Examine the relationship between the use of LLT at randomization and short- (4 years) and long-term (11 years) all-cause and CVD mortality by absolute CVD risk in those aged 65 years or over.

  Chapter 5 presents a post-hoc observational analysis of the Second Australian National Blood Pressure Study (ANBP2). ANBP2 is a comparative trial of two treatment arms (diuretic and ACE-I) with an open-labelled design with the blinded end-point assessment. The participants would be reclassified to LLT and no LLT group based on their treatment status before enrolling in the ANBP2 trial. ANBP2 was selected due to its large sample size and extended follow-up including post-trial phase up to 11 years.

  Cox proportional hazard models were used to estimate the hazard ratios and corresponding 95% confidence interval (CIs) for outcomes for participants in the ‘‘LLT’’ group compared with those in ‘‘no LLT’’ group. All of the analyses were adjusted by baseline and in-trial characteristics. A subgroup analysis was conducted using the tertile of 5-year FRS. The Cox regression models were used to test for interaction of treatment in the subgroup analyses.

  Similar to the study conducted in chapter 3, the results of this study were impacted by the risk of ‘confounding by indication’ where physicians

tended to prescribe lipid lowering drug treatment on those with higher underlying CVD risk. The results should be interpreted carefully.

Structure of this thesis

Chapter 1: Introduction

Chapter 2: Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: Post-hoc analysis of the Australian National Blood Pressure Study.

Chapter 3: Legacy effect of baseline blood pressure 'treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

Chapter 4: Legacy effect of delayed blood pressure lowering drug treatment in middle-aged adults with mildly elevated blood pressure: systematic review and meta-analysis.

Chapter 5: Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure Study (ANBP2).

Chapter 6: Summary, implications, future directions and conclusions

Concluding remarks

This chapter provides some backgrounds on the burden and primary prevention of CVD. Generally, this chapter points out that (1) Primary prevention based on absolute risk approach is more cost-effective than traditional risk approach with threshold alone (e.g. blood pressure or blood cholesterol) (2) BP lowering drug treatment is reserved to the high-risk setting with BP threshold of 130/90 mmHg or higher. Benefits and harms of drug treatment in individuals at low-moderate risk with or without mildly elevated BP are controversial. (3) Lipid-lowering drug treatment, particularly statins are generally prescribed in elderly populations due to its dominant effects on non-fatal CVD outcomes whereas the survival benefits are less clear. (4) Most of the current evidence is attributable to studies with less than five years of follow-up. The preventive treatment is a lifelong therapy, thus its long-term effects should be taken into consideration.

Chapter 2

Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: A Post-hoc analysis of the Australian National Blood Pressure Study.

Published in the journal

BMJ Open 2018; 8(3):e017723.

Chau L.B Ho, Monique Breslin, Jenny Doust,

Christopher M. Reid, Mark R. Nelson

Chapter 2 Effectiveness of Blood Pressure-Lowering Drug Treatment by Levels of Absolute Risk: A Post-hoc analysis of the Australian National Blood Pressure Study.

Preface

In an attempt to assess which group of 'mild hypertensive' individuals classified by absolute risk benefits from actively BP lowering drug treatment, this chapter presents an analysis on the Australian National Blood Pressure study (ANBP), a seminal study in 'mild hypertensive' persons in 1970s. ANBP was a randomised placebo-controlled trial that provided a great opportunity to compare the impacts of early versus delayed treatment. This could not be done in modern clinical trials when placebo-controlled is unlikely to be ethical.

The following text in this chapter was published in the journal BMJ Open 2018; 8(3):e017723.

Abstract

Objectives: In many current guidelines, blood pressure (BP)-lowering drug treatment for primary prevention of cardiovascular disease (CVD) is based on absolute risk. However, in clinical practice, therapeutic decisions are often based on BP levels alone. We sought to investigate which approach was superior by conducting a post hoc analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons.

Design: A post hoc subgroup analysis of the ANBP trial results by baseline absolute risk tertile.

Setting and participants: 3244 participants aged 35–69 years in a community-based randomised placebo-controlled trial of blood pressure-lowering medication.

Interventions: Chlorothiazide500 mg versus placebo.

Primary outcome measures: All-cause mortality and nonfatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).

Results Treatment effects were assessed by HR, absolute risk reduction and number needed to treat. Participants had an average 5-year CVD risk in the intermediate range (10.5±6.5) with moderately elevated BP (mean 159/103mmHg) and were middle-aged (52±8 years). In a subgroup analysis, the relative effects (HR) and absolute effects (absolute risk reduction and number needed to treat) did not statistically differ across the three risk groups except for the absolute benefit in all-cause mortality (p for heterogeneity=0.04). With respect to absolute benefit, drug treatment significantly reduced the number of events in the high-risk group regarding any event with a number needed to treat of 18 (10 to 64), death from any cause with 45 (25 to 196) and major CVD events with 23 (12 to 193).

Conclusion: Our analysis contributed further evidence that the benefit of treatment was substantial only in the high-risk tertile, reaffirming the rationale of treating elevated blood pressure in the setting of all risk factors rather than in isolation.

Introduction

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world [161, 162]. In 2012, CVD was responsible for 17.5 million deaths in the world and more than twenty thousand deaths in Australia[161, 163]. Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the commonest modifiable population risk factor[164]. Drug therapy for primary prevention of CVD is now recommended to be based on absolute CVD risk, where BP lowering drug treatment is determined by BP level together with other major CVD risk factors (e.g. sex, age, total cholesterol, high-density lipoprotein cholesterol, diabetes and smoking status) as an integrated score[2, 3, 40, 165, 166].

Yet clinicians are reticent to treat systolic BP in those below 140 mmHg at high risk as well as not treating patients at low risk with blood pressure above this threshold. There is a paucity of literature on the effects of lowering BP in low to moderate CVD risk individuals with Grade 1 hypertension (systolic BP from 140 mmHg to 159 mmHg and/or diastolic BP from 90 to 99) and some debate regarding its benefit[105]. Guidelines from the US and Europe tend to promote early drug treatment due to the potential benefits of earlier intervention and potential adverse effects of delayed intervention [40, 41, 59, 63, 165-168]. However JNC 8 [41] recommends initiating drug treatment at the threshold of 150 mmHg systolic BP or 90 mmHg diastolic BP for the general population at 60 years or older. This revised recommendation has caused controversy amongst clinicians who argue that drug treatments need to be initiated at a lower systolic BP of 140 mmHg, as previously recommended in JNC 7[169], otherwise patients are exposed to increased risk[110, 170-172]. Similarly, the 2018 European Society of Cardiology guidelines recommends considering BP lowering drug treatment when systolic BP is greater than 140 mmHg and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with lifestyle choice[59]. Recently, the SPRINT (Systolic Blood Pressure Intervention trial)[92] reported a significant benefit from intensive treatment to a target BP of 120 mmHg rather than 140 mmHg. However, this benefit was observed in those at high CVD risk without diabetes. In agreement with the findings from the SPRINT trial, guidelines in Australia[2], New Zealand[1], UK[166] and Canada[3] recommend BP lowering medication based on absolute CVD risk, recommending BP lowering treatment as soon as possible in high CVD risk individuals, but not in the low to moderate risk population unless BP persistently exceeds 160/100 mmHg.

Other groups[173] have recommended early drug treatment of grade 1 hypertension even in patients at low risk with the exception of patients with grade 1 “isolated” hypertension, based on a meta-analysis by Thomopolous et al[89] and the HOPE-3 study[97]. In contrast, a Cochrane review by Diao et al[105] concluded that there was no statistically significant effect of BP treatment in individuals who had grade 1 hypertension. The 2015 Blood Pressure Lowering Treatment Trialists Collaboration[88] (BPLTTC) meta-analysis reported a statistically significant benefit of BP lowering drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality. However, the effects seen in the BPLTTC analysis could reflect differences in the BPLTTC sample that included participants who had diabetes, had a higher baseline risk and had previously received drug treatment. In another analysis of the BPLTTC individual patient data[84] by absolute CVD risk at baseline showed a continuously increasing benefit with baseline risk. The BPLTTC study, however, included participants who both did and did not have a history of CVD.

Thus, we sought to reanalyse a seminal study used to justify treating individuals with elevated BP to see if stratification by baseline CVD risk would be a superior method for identifying candidates for BP-lowering medication in a treatment-naïve population. In this study, we compared the effectiveness of BP lowering drug treatment by a post-hoc subgroup analysis of the Australian National Blood Pressure study[174] (ANBP). We restricted the analysis group to individuals with no history of CVD or diabetes, and who were naïve to BP lowering treatment. We selected this historic study because it was placebo-controlled and patients in the control arm of the study would not have been taking a BP lowering medication previously unless they had very high levels of

BP. Our aim was to assess which group of individuals classified by absolute risk benefited from active treatment vs. placebo for CVD events within this seminal study that underwrote the treatment of elevated BP by BP thresholds.

Methods

Study design and population

We performed a post-hoc analysis of the Australian National Blood Pressure study (ANBP)[174]. ANBP was conducted between 1973 and 1979 in Melbourne, Perth and Sydney and was a multicentre, single-blind placebo randomised controlled trial. ANBP enrolled participants who had not been on treatment for hypertension in the past three months and had no history of CVD or diabetes. In the 1970s, 'mild hypertension' was defined as a screening diastolic BP of 95 to 109 mmHg with a systolic BP lower than 200 mmHg. At the screening phase, mean of two BP readings were assessed at two separate visits at 1-2 weeks intervals. The measurements were conducted by non-medical staffs using random-zero sphygmomanometers at standardised criteria. 104171 participants were screened, 3931 eligible participants were initially randomised, then 504 participants were excluded because their BP throughout the study did not meet the criteria for starting drug treatment (entry or follow-up diastolic BP higher than 95 mmHg and/or entry or follow-up systolic BP higher than 200 mmHg) (Figure 2.1)

Included participants were randomised to chlorothiazide 500mg or placebo that was identical in appearance with the active agent, with stratification by age and sex. When a systolic BP or diastolic BP exceeded 200 and 110 mmHg respectively at three visits within 6 weeks, participants in the placebo group would be prescribed active treatment. The study intervention remains applicable to current practice as thiazide diuretics (e.g. hydrochlorothiazide) are still first line BP lowering agents[2, 3, 40, 166, 175]. The first step of active treatment was 500 mg chlorothiazide daily, then the dose was

increased to 500 mg chlorothiazide twice daily or second agents (e.g. alpha-methyldopa, propranolol or pindolol) or thirds agents (e.g. hydralazine or clonidine) were added to achieve the treatment target of 80 mmHg of diastolic BP. All participants were advised on weight, diet and exercise.

The primary endpoints were all-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy)[174].

Risk stratification

In this analysis, the baseline absolute CVD risk was calculated according to the 5-year Framingham absolute risk score[43]. The Framingham score was chosen because it is currently recommended in the National Vascular Disease Prevention Alliance (NVDPA) guidelines[2] in Australia. The sample was restricted to 3,244 participants who were older than 35 years and was stratified by tertile of estimated 5-year CVD risk score (Figure 2.1). We also classified all participants with very high BP (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg) or total cholesterol (> 7.5 mmol/l) values the highest risk tertile regardless of their risk score, as per the Australian guidelines[2]. The ANBP dataset included all variables required for CVD risk calculation except high-density lipoprotein cholesterol (HDLc). The HDLc value was imputed from the Australian National Heart Foundation risk factor prevalence study as this was near contemporaneous with the ANBP[176]. Mean value of HDLc was categorised by age and sex. In a sensitivity analysis, we stratified the sample by GLOBORISK score[177], a CVD risk score that does not require HDLc value and is validated in individuals over 40 years. The equation for the Australian population was obtained by personal contact with the author (Peter Ueda, unpublished data, 2016). This analysis excluded 471 participants younger than 40 years. Less than 1% of the study participants had data missing for total cholesterol, weight and/or height and these missing data were managed by multiple imputations using chained equations.

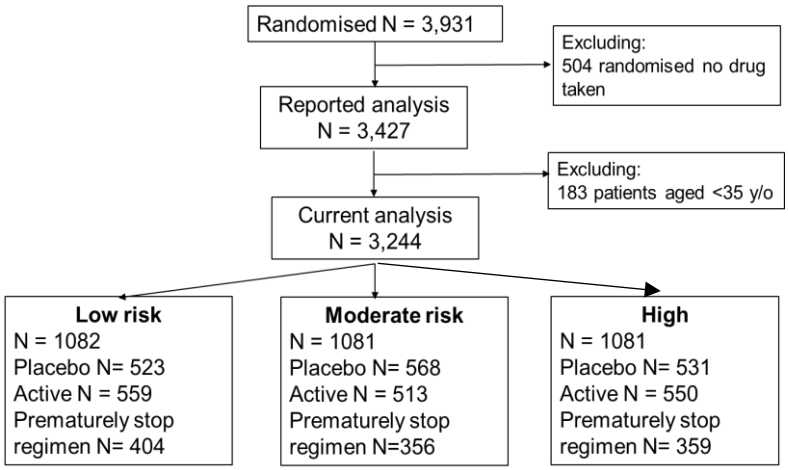


Figure 2.1. Trial profile.

Statistical analysis

All analyses were based on the modified 'intention to treat' principle. We included participants who had withdrawn from the study by their group allocation at randomisation in all analyses. The differences in baseline characteristics between 'active group' and 'placebo group' were tested by ANOVA test for continuous variables and Chi-square test for categorical variables. Treatment effects were assessed by hazard ratio (HR), absolute risk reduction (ARR) and number needed to treat (NNT). The HRs and corresponding 95% confidence intervals were estimated by Cox proportional hazard model after adjusting for clustering of participants within community-based centers and potential risk factors including baseline characteristics. The proportional assumption was checked by the test for interaction of HR with time. ARR and NNT were estimated from Kaplan-Meier curves at the median of follow-up time (4.4 years)[178]. Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the Hazard ratio and a Cochran's Q test for the absolute risk reduction. The threshold for significance

for treatment effect was set at 0.05 for the main analysis and subgroup analysis. Only one subgroup analysis with related outcomes was conducted, thus multiplicity was not likely to affect our results.

Ethics approval. This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015252).

Results

Patient characteristics

Table 2.1 provides baseline characteristics of the participants stratified by the tertile of the CVD risk score. On average, study participants had intermediate 5-year CVD risk as referred in the NVDPA guideline (10.5 ± 6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle-aged (52± 8). The tertiles had estimated 5-year CVD risks of less than 6.1% (low), 6.1 to 17.0% (moderate) and more than 17.0% (high). These values are similar to the thresholds recommended by the Australian NVDPA guideline[2] for low (<10%), moderate (10-15%) and high-risk categorisation (>15%). A stratification by these cut-off points was attempted, but the number of participants in each subgroup were substantially imbalanced (2757 low risk participants, 422 moderate risk participants and 65 high risk participants) and the number of events in the high risk group were not high enough to run an analysis. The distribution of baseline characteristics by treatment assignment was not significantly different except for body mass index (BMI) in the total population, the number of smokers in the low-risk group, systolic BP and BMI in the moderate risk group.

Table 2.1. Baseline characteristics stratified by tertile of baseline CVD risk score.

Group variable	Total	Low (<6.1 %)	Moderate (6.1 – 17.0%)	High (>17.0%)
Sample, N	3244	1082	1081	1081
Randomised to active treatment, N (%)	1622 (50%)	559 (51.7%)	513 (47.5)	550 (50.9)
Age, years	51.7 ± 8.1	46.0 ± 6.2	54.5 ± 6.5	54.6 ± 8.1
Male sex, N (%)	2017 (62.2)	567 (52.4)	804 (74.4)	646 (59.8)
Current smoker, N (%)	801 (24.7)	**115 (10.6)**	352 (32.6)	334 (30.9)
SBP, mmHg	159.5 ± 17.5	148.4 ± 12.2	**157.3 ± 12.2**	172.6 ± 17.9
DBP, mmHg	102.9 ± 6.8	100.0 ± 3.8	100.8 ± 4.4	107.9 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.5 ± 1.3
BMI, kg/m2	**26.6 ± 3.9**	26.6 ± 4.0	**26.5 ± 3.6**	26.7 ± 4.1

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold** $p<0.05$ based on the distribution of baseline characteristics by treatment assignment.

Approximately one-third of the participants (34.5%) prematurely stopped study treatment due to decisions by clinics, participants' doctors, and the participant themselves, or for unknown reasons (Table 2.2). Participants' doctors were more likely to stop placebo treatment in all three risk groups, whereas clinics withdrew more BP-lowering drug-randomised participants in the low-risk group and the high- risk group. No substantial difference in baseline characteristics between the two randomised treatment groups was recorded in any risk group.

Table 2.2. Characteristics of those who prematurely stopped study regimen.

Group variable	Total	Low (<6.1%)	Moderate (6.1-17.0%)	High (>17.0%)
Sample, N	1119	404	346	369
Randomised to active treatment, N (%)	531 (47.5)	204 (50.5)	151 (43.6)	176 (47.7)
Age, years	51.2 ± 8.3	45.9 ± 6.4	54.1 ± 7.0	54.2 ± 8.5
Male sex, N (%)	626 (55.9)	188 (46.5)	243 (70.2)	195 (52.9)
Current smoker, N (%)	321 (28.7)	58 (14.4)	143 (41.3)	120 (32.5)
SBP, mmHg	159.1 ± 18.1	147.6 ± 12.9	157.0 ± 11.9	173.7 ± 17.7
DBP, mmHg	102.9 ± 6.8	100.0 ± 4.0	100.6 ± 4.2	108.1 ± 8.2
Total cholesterol, mmol/l	6.0 ± 1.1	5.5 ± 0.9	6.0 ± 0.9	6.4 ± 1.3
BMI, kg/m2	26.7 ± 4.1	26.7 ± 4.0	26.6 ± 3.9	26.8 ± 4.5
Reason for stopping				
Clinic, N (%)	204 (18.2)	**74 (18.3)**	75 (21.7)	**55 (14.9)**
Local doctor, N (%)	287 (25.7)	**98 (24.3)**	**87 (25.1)**	**102 (27.6)**
Participants, N (%)	548 (49.0)	204 (50.5)	162 (46.8)	182 (49.3)
Not known, N (%)	80 (7.2)	28 (6.9)	22 (6.4)	30 (8.1)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index. **Bold** $p<0.05$ based on the distribution of baseline characteristics by treatment assignment.

Effect of BP lowering drug treatment on the total study population

During a median follow-up of 4.4 years (IQR 1.0 – 5.9), 257 major CVD events (7.9%) were observed, in which ischemic heart disease accounted for 203 events (6.3%), stroke 48 events (1.5%) and congestive heart failure 6 events (0.2%).

After adjustment for sex, age, BMI, smoking, systolic BP at baseline and study centres, BP lowering treatment was associated with a 15% reduction in non-fatal events and a 25% reduction in all-cause mortality (Figure 2.2), although the treatment effects were not statistically significant. Similar effects were found in the secondary endpoints including any events HR 0.82 (0.65 – 1.03), major CVD events HR 0.83 (0.65 – 1.07) and non-fatal CVD events HR0.87 (0.67 – 1.13). We identified a marginally significant effect in stroke HR 0.55 (0.3 – 1.001).

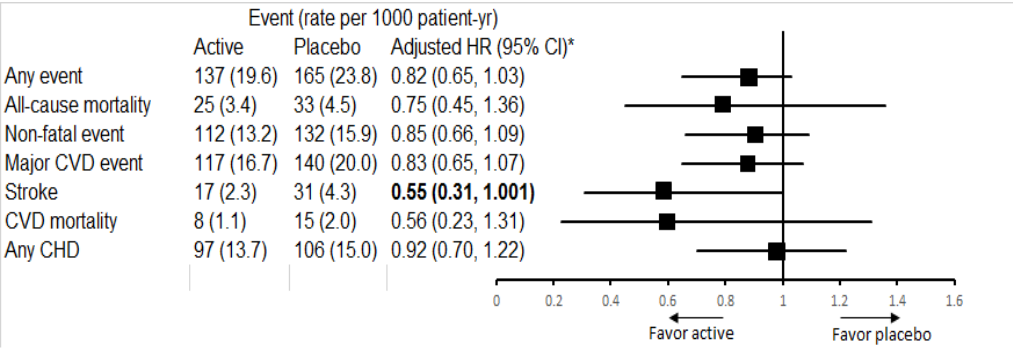


Figure 2.2. Effect of treatment in the overall study population.

*Adjusted for age, sex, body-mass index, screening centres, smoking and systolic blood pressure. **Bold** p<0.05. CVD for cardiovascular disease, CHD for coronary heart disease.

Effect of BP lowering drug treatment on 5 year-CVD risk groups

In the subgroup analysis, the magnitude of relative treatment effect increased from low to high CVD risk group, though the benefits were not statistically significant in the high-risk group in terms of all-cause mortality 0.60 (0.26 - 1.40) and major CVD event with HR 0.76 (0.52 - 1.10).

The increasing trend for the benefit was also observed when comparing the absolute treatment effects absolute risk reduction – ARR among the three risk groups. No evidence of heterogeneity was observed except the effect in all-cause mortality. Substantial effects of BP lowering treatment were produced in the high-risk group regarding any trial endpoints (ARR 5.6 (1.6, 9.6)), all-cause mortality (ARR 2.2 (0.5, 3.9)) and any CVD event (ARR 4.3 (0.5, 8.1)) (Table 2.3). Treating 18 high-risk participants for 4 years prevented one trial event, treating 45 prevented one death and treating 23 prevented one CVD event. In contrast, treating low or moderate risk participants needed much higher numbers to prevent one event or possibly caused net harm (Table 2.3). Similarly, in the subgroup analysis by tertile of baseline SBP (Appendix), active treatment group was also associated with significant absolute risk reduction on any trial endpoint (ARR 4.8 (0.9, 8.8)), all-cause mortality (ARR1.9 (0.3, 3.6)) and any CVD event (ARR 4.1 (0.4, 7.8)), however no statistically significant heterogeneity was recorded in any outcomes. Also, a sensitivity analysis by using the GLOBORISK score[177] which does not require HDLc was consistent with our original findings, except that the absolute risk reduction in major CVD event is no longer statistically significant with ARR 3.4% (-0.4,7.3, p = 0.08).

Table 2.3. Effect of treatment by tertile of baseline CVD risk score.

	Active	Placebo			
	Event (rate per 1000 patient-yr)		Adjusted HR (95% CI)*	ARR % (95% CI)**	NNT**
Any event					
Low	22 (8.9)	23 (10.0)	0.94 (0.52 - 1.70)	-0.3 (-2.7, 2,1)	-370 (-37, 47)
Moderate	56 (26.1)	67 (28.0)	0.93 (0.65 - 1.33)	1.1 (-2.9, 5.2)	87 (-34, 19)
High	59 (24.8)	75 (33.2)	0.75 (0.53 - 1.06)	**5.6 (1.6, 9.6)**	**18 (10, 64)**
p - value	-	-	0.64	0.05	-
All-cause mortality					
Low	6 (2.4)	6 (2.5)	0.96 (0.30-3.01)	-0.5 (-1.6, 0.7)	-213 (-63, 153)
Moderate	10 (4.4)	13 (5.1)	0.81 (0.35 - 1.86)	0.2 (-1.7, 2.1)	476 (-60, 48)
High	9 (3.5)	14 (5.7)	0.60 (0.26 - 1.40)	**2.2 (0.5, 3.9)**	**45 (25, 196)**
p – value	-	-	0.78	**0.04**	-
Non-fatal event					
Low	16 (6.4)	17 (7.4)	0.93 (0.47 - 1.87)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	46 (21.3)	54 (22.2)	0.96 (0.65 - 1.43)	0.9 (-2.8, 4.5)	118 (-35, 22)

	Active	Placebo			
	Event (rate per 1000 patient-yr)		Adjusted HR (95% CI)*	ARR % (95% CI)**	NNT**
High	50 (20.9)	61 (26.6)	0.80 (0.55- 1.16)	3.3 (-0.4, 7.0)	30 (-249, 14)
p – value	-	-	0.77	0.36	-
Major CVD event					
Low	17 (6.8)	18 (7.8)	0.98 (0.50 - 1.91)	0.2 (-1.9, 2.3)	476 (-52, 43)
Moderate	50 (23.2)	58 (24.0	0.98 (0.67 - 1.43)	0.6 (-3.2, 4.5)	164 (-31, 22)
High	50 (20.9)	64 (28.0)	0.76 (0.52 - 1.10)	**4.3 (0.5, 8.1)**	**23 (12, 193)**
p - value	-	-	0.62	0.17	-
Any CHD					
Low	17 (6.8)	14 (6.0)	1.21 (0.59 - 2.48)	-0.4 (-2.4, 1.6)	-256 (-41, 61)
Moderate	39 (17.9)	47 (19.2)	0.93 (0.60 - 1.42)	1.1 (-3.0, 5.1)	94 (-33, 19)
High	41 (17.0)	45 (19.2)	0.90 (0.59 - 1.37)	1.9 (-1.4, 5.3)	52 (-72, 19)
p - value	-	-	0.83	0.47	-

CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ARD: absolute risk difference, NNT: number needed to treat. NNTB: number needed to treat (benefit). NNTH: number needed to treat (harm).p-value indicated p for interaction.

* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure. ** As estimated by the Kaplan-Meier curve. Bold p<0.05

Discussion

Our study population had an overall moderate 5-year CVD risk (10.5%) and moderately elevated systolic BP (mean 159/103 mmHg) by modern definitions. The ANBP study aimed to treat 'mild hypertension' (according to the old definition) that was primarily defined by diastolic BP. Some randomised participants were excluded from the original analysis because they did not meet the criteria for starting BP lowering drug treatment post-randomisation. This would not be seen in modern clinical trials. In our reanalysis, we found that BP lowering drug treatment reduced the risk of major CVD events and all-cause mortality, but the effect was not statistically significant. This is likely to be due to reduced power as the cohort was analyses by tertile of absolute risk, as well as by the two groups of randomised therapy. The original study found a statistically significant reduction in the incidence of CVD mortality and all trial endpoints, using the full dataset and a risk ratio rather than time-to-event analysis[174].

In our analysis of subgroups defined by CVD risk score, the magnitude of relative treatment effects (relative risk reduction) on all-cause mortality and major CVD events increased across all three CVD risk group from low to high risk, without statistically significant heterogeneity ($p = 0.78$ for all-cause mortality and $p = 0.62$ for the major CVD event) (Table 2.3). It is expected that the p value for interaction does not reach significance here, due to the low number of events, and the requirement for a much larger sample for adequate power to detect subgroup interactions than for a main effect [179]. All relative treatment effects in our analysis measured by HRs were adjusted by age, sex, body-mass index, smoking, screening centres and systolic BP. However, no

significant difference was observed between adjusted and unadjusted HRs probably because randomisation successful balanced these characteristics between groups. In terms of absolute benefits, risk reduction linearly increased across the CVD risk group from low to high risk. . BP lowering drug treatment produced an unclear benefit in the low and intermediate CVD risk group, and a clinically meaningful benefit in the high CVD risk group

Regarding the benefit of BP lowering drug treatment in the low to intermediate CVD risk population, our results from main and subgroup analyses match well with the study outcomes from the HOPE-3 trial[97], the Diao review[105] and a retrospective observational study by Sheppard et al[106]. In the HOPE-3 trial[97], no benefit of intensive drug treatment was established in the intermediate-risk persons with HR 0.98 (0.84-1.14) for all-cause mortality and HR 0.92 (0.79 – 1.06) for major CVD events referred as a first secondary outcome in the paper. At baseline, the HOPE-3 participants were older (65 years) and had a lower level of BP (138.1/81.9 mmHg) compared to the ANBP participants. One reason for the lower blood pressures may be due to the 4-week run-in phase in which all of the HOPE-3 participants received active BP lowering drug treatment before randomisation and one-fifth of all eligible participants had previously received drug treatment before the trial. Similarly, Sheppard et al also observed a non-signification association between BP lowering drug treatment and mortality or major CVD event with a RR 1.02 (0.88-1.17) and a RR 1.09 (0.95-1.25) respectively in a low risk population. Participants in this study had a lower average BP 146/89 mmHg than our participants. However, the BP value in the treated group was likely to be underestimated. In 2012, Diao et al reviewed placebo randomised controlled

trials in grade 1 hypertension and also found no beneficial effect of drug treatment with a risk ratio (RR) 0.85 (0.63 – 1.15) for all-cause mortality and RR 0.97 (0.2 – 1.32) for major CVD events[105]. The participants in the Diao review were likely to have a lower CVD risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring in only 2.4% of participants in the placebo group. Following a similar approach, in 2015, The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC)[88] reviewed randomised controlled trials in grade 1 hypertension but extended to trials comparing active or more intensive regimens and placebo or less intensive regimens. In line with the findings from the 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45 – 1.36) for total deaths and an HR 0.83 (0.65 – 1.07) for major CVD events slightly differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67-0.92) and an OR 0.86 (0.74-1.01) correspondingly. The differences in confidence intervals may be due to the difference in sample sizes and baseline characteristics. It is more likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at baseline when about 40% of 15,266 participants had diabetes and about 23% had previously received BP lowering drug treatment. Our study and the 2015 review confirm the absolute benefits of BP lowering drug treatment in high CVD risk population in terms of total deaths with ARR 2.2% (0.5, 3.9, p=0.01) for the ANBP and ARR 1.4% (0.5, 2.2) for the review. Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5, 8.1, p=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant effect with ARR 1.0% (-0.1, 1.9). The difference can be explained in part by the study design when more than 50% of participants with systolic BP higher than

160 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of these excluded participants might not be even between active arm and control arm, thus biasing the treatment effects.

In another subgroup analysis stratified by tertile of baseline systolic BP (Appendix), the mean value of CVD risk varied from low to high corresponding to the lowest and the highest tertile. The relative treatment benefits were not statistically significant, but in terms of absolute effects, BP lowering drug treatment substantially reduced any trial events, all-cause mortality and major CVD events within the highest tertile. The findings were in line with what we found in the CVD risk-stratified subgroup when all participants in the highest BP-stratified tertile had a high CVD risk score (20.7 ± 9.5). However, the heterogeneity of treatment effects among the three subgroups in the analysis by baseline systolic BP was no longer significant as it was in the subgroup analysis by CVD risk score. Further, the trend of lower to higher absolute benefit from low to high-risk groups that was seen for CVD risk was not apparent when groups are defined by BP alone. Thus, in this study, the CVD risk score identified those who most benefited from BP lowering drug treatment.

Limitations

There are a number of limitations of our study. Firstly, statistical power is unavoidably decreased in a post-hoc subgroup analysis. The multivariate Framingham risk score used in our analysis has not been well validated within the Australian population[180], however it remains the most well-established and accepted method for CVD risk assessment[181]. Using a multivariate score for stratification is known to increase the power to detect heterogeneity in absolute

risk benefit over subgroup analyses that are based on individual risk factors[182]. A prospective study to address the issue of whether there is an advantage in treating blood pressure by AR is unlikely to be performed, because of the very large sample size and very long follow-up time required, particularly in patients at low risk. Therefore, re-analysis of the early placebo-controlled trials seems to be the most feasible approach for assessing the effects of delayed versus early drug treatment in individuals with varying CVD risk together and elevated BP. A large scale observational data may be another optimal approach.

Secondly, the estimation of HDLc from the 1980s national survey may alter the CVD risk score, but we do not believe this method greatly affected the risk stratification because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD risk score. Furthermore, no association between HDLc and BP has been observed[183, 184]. The sensitivity analysis using GLOBORISK score[177] without HDLc showed similar results as our main analysis. Although the ARR is no longer statistically significant, this result is likely due to the smaller sample size and subsequent number of events. In conclusion, the sensitivity analysis supports our main analysis.

Thirdly, the paucity of trial endpoints in each CVD risk group prevented us from comparing the effects in some specific outcomes with respect to stroke and deaths from CVD. In addition, approximately one-third of the participants prematurely stopped randomised drug treatment. However, this pattern likely reflects the typical situation to occur in actual clinical practice, and this analysis is conducted on an intention-to-treat basis, so any difference in the estimate of treatment effect due to non-adherence is deliberately retained. Most participants were followed throughout the trial, except those with an unknown

reason for stopping - loss to follow-up (7.2%). An analysis with further adjustment by variable 'premature stopped study treatment' did not substantially change our findings, except effects on stroke in general population became statistically significant (0.55, 95%CI 0.30-0.99, p=0.05). This is because non-adherence is balanced between the allocated treatment groups.

In conclusion, our research has contributed further evidence that drug treatment in patients with elevated BP should be directed to those at high risk of incident CVD events. This reinforces the guidelines recommendation to treat based on absolute (or global) CVD risk, rather than according to BP thresholds alone[2, 3, 40, 166, 175].

Postscripts

This chapter contributed justifications for treating high blood pressure established on an absolute risk approach that accounts for other major CVD risk factors. The next chapter examined the 14-year 'legacy effect' of not treating high blood pressure in individuals without established CVD.

Appendix

Table appendix 2.1. Baseline characteristics stratified by tertile of baseline systolic blood pressure

Group variable	1st tertile (113-151 mmHg)	2nd tertile (152 – 165 mmHg)	3rd tertile (166 – 225 mmHg)
Sample, N	1156	1014	1074
Age, years	48.8 ± 7.3	51.4 ± 7.8	55.1 ± 7.8
Male sex, N (%)	803 (69.5)	645 (63.6)	569 (53.0)
Current smoker, N (%)	285 (24.7)	251 (24.8)	265 (24.7)
SBP, mmHg	142.1 ± 7.0	158.2 ± 3.9	179.3 ± 11.7
DBP, mmHg	99.7 ± 4.1	102.7 ± 6.0	106.5 ± 8.0
Total cholesterol, mmol/l	5.9 ± 1.1	6.0 ± 1.1	6.1 ± 1.2
BMI, kg/m2	26.7 ± 3.6	26.5 ± 3.7	26.6 ± 4.4
CVD risk (%)	7.9 ± 8.7	12.8 ± 9.6	20.7 ± 9.5

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body - mass index, CVD: cardiovascular disease.

Table appendix 2.2 Effect of treatment by tertile of baseline systolic blood pressure

	Event (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Any event					
113-151 mmHg	34 (5.6)	43 (7.8)	0.71 (0.45 -1.11)	2.5 (-0.7,5.6)	41 (-135, 18)
152 – 165 mmHg	49 (9.8)	46 (9.0)	1.07 (0.71 - 1.61)	-1.2(-5.0, 2.7)	-87 (-20, 37)
166 – 225 mmHg	54 (10.5)	76 (3.6)	0.73 (0.51-1.03)	**4.8 (0.9, 8.8)**	**21 (11, 112)**
p-value	-	-	0.25	0.1	-
All-cause mortality					
113-151 mmHg	5 (0.8)	10 (1.8)	0.49 (0.17-1.46)	0.7 (-0.2, 1.7)	139 (-468, 60)
152 – 165 mmHg	11 (2.2)	8 (1.6)	1.30 (0.51 - 3.28)	-0.9 (-2.7, 0.9)	-110 (-36, 108)
166 – 225 mmHg	9 (1.7)	15 (2.7)	0.64 (0.28 - 1.46)	**1.9 (0.3, 3.6)**	**52 (28, 372)**
p – value	-	-	0.26	0.08	-
Non-fatal event					
113-151 mmHg	29 (4.8)	33 (6.0)	0.77 (0.47 - 1.28)	1.2 (-1.7, 1.5)	86 (-59, 25)
152 – 165 mmHg	38 (7.6)	38 (7.4)	1.00 (0.63 - 1.58)	-0.2 (-3.6, 1.7)	-455 (-27, 31)
166 – 225 mmHg	45 (8.7)	61 (10.9)	0.76 (0.52 - 1.13)	2.9 (-0.8, 1.8)	35 (-133, 15)
p – value	-	-	0.58	0.48	-

	Event (%)				
	Active	Placebo	Adjusted HR (95% CI)*	ARR % (95% CI)	NNT
Major CVD event					
113-151 mmHg	31 (5.1)	35 (6.3)	0.79 (0.48 - 1.28)	1.6 (-1.3, 1.5)	61 (-74, 22)
152 – 165 mmHg	41 (8.2)	40 (7.8)	1.04 (0.67 - 1.61)	-0.4 (-4.0; 3.1)	-227 (-25, 32)
166 – 225 mmHg	45 (8.7)	65 (11.7)	0.73 (0.50 - 1.06)	**4.1 (0.4, 7.8)**	**24 (13, 242)**
p - value	-	-	0.39	0.22	-
Any CHD					
113-151 mmHg	30 (5.0)	29 (5.3)	0.93 (0.56 - 1.56)	0.4 (-2.4, 3.1)	286 (-42, 32)
152 – 165 mmHg	29 (5.8)	30 (5.9)	0.95 (0.57-1.59)	-0.1 (-3.1, 2.9)	-1250 (-32, 34)
166 – 225 mmHg	38 (7.4)	47 (8.4)	0.87 (0.57-1.34)	2.0 (-1.4, 5.4)	51 (-71, 19)
p - value	-	-	0.89	0.65	-

CVD: cardiovascular disease, CHD: coronary heart disease, HR: hazard ratio, CI: confidence interval, ARD: absolute risk difference, NNT: number needed to treat. p-value indicated p for interaction.

* Adjusted for age, sex, body-mass index, smoking, screening centres and systolic blood pressure. **Bold** p<0.05

Chapter 3

Legacy effect of baseline blood pressure 'treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Published in the journal
Journal of Hypertension 2019 (Epub ahead of print)
Chau LB Ho, Monique Breslin, Enayet K Chowdhury,
Jenny Doust, Christopher M Reid,
Barry R Davis, Lara M Simpson & Mark R Nelson

Chapter 4

Legacy effect of delayed blood pressure lowering drug treatment in middle-aged adults with mildly elevated blood pressure: Systematic review and meta-analysis

Plan to submit to Journal of Hypertension

Chau L. B. Ho, Sharon Sanders, Monique Breslin, Jenny Doust,

Christopher M. Reid, Barry R. Davis, Lara M. Simpson,

Frank P. Brouwers, Rudolf A. de Boer, Mark R. Nelson

Chapter 4 Legacy effect of delayed blood pressure lowering drug treatment in middle-aged adults with mildly elevated blood pressure: systematic review and meta-analysis.

Preface

The previous chapter showed no significantly increased risk of all-cause and CVD mortality of baseline BP treatment naivety over a 5 and 14-year periods at any level of CVD risk stratification. This chapter would investigate the 'legacy effects' of no BP lowering drug treatment in a relatively lower risk population who had mildly elevated BP at middle age.

Abstract

Objective

To investigate if there is evidence for a 'legacy effect' for blood pressure lowering treatment, that is worse health outcomes from not initiating drug treatment at a systolic blood pressure (SBP) threshold of 140 mmHg in middle-aged adults.

Methods

We systematically reviewed post-trial studies comparing the effects of delayed BP treatment (placebo/untreated during the trial or no previous treatment at trial entry) versus early treatment (actively treated during the trial or previous BP treatment at trial entry) on mortality in the short-term (5-year in-trial period) and long-term (≥10 years in total period). The data were pooled using Peto odds ratio . A subgroup analysis by 10-year Framingham risk score was performed.

Results

Three studies (ALLHAT, Oslo and PREVEND-IT) involving 4746 participants were included. The results were heavily influenced by the ALLHAT trial. We found no significant difference in all-cause mortality between 'delayed BP' and 'early treatment' in the short-term OR 0.95 (95% CI 0.68- 1.32) or long-term OR 0.90 (95%CI 0.78-1.04), with similar results for

mortality from cardiovascular disease (CVD). The effects of delayed BP lowering treatment on long-term all-cause and CVD mortality did not vary with baseline risk of CVD.

Conclusion

The review showed no clinically adverse 'legacy effect' on mortality or major CVD event from not treating middle-aged adults at a systolic BP threshold of 140 mmHg or over. The results were consistent for all CVD risk subgroups. Although these studies are non-randomised post-hoc analyses, they may allay concerns that early treatment of elevated SBP is necessary to prevent CVD events.

Introduction

The effectiveness of blood pressure lowering drugs to prevent cardiovascular disease (CVD) has been well established in trials of patients with diabetes, the elderly, or those with a SBP of ≥160 mmHg or over (for example SHEP, Syst-Eur, HYVET and UKPDS). However, there remains a lack of evidence for the effects of BP lowering pharmacotherapy in middle-aged adults with mildly elevated BP. A recent systematic review by Diao et al [105] on participants with systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg found a no statistically significant effect of active treatment on the reduction of CVD or deaths. However, a similar review by the Blood Pressure Lowering Treatment Trialist's Collaboration (BPLTTC)[88] observed significant reductions in stroke, CVD and all-cause deaths. Although the BPLTTC review included more trials with larger number of participants, the review included trials with less versus more intensive treatments and trials with new blood pressure treatment added to pre-existing medication and so the comparison was not restricted to active versus placebo/no treatment as in the Diao et al review. In line with the finding in the Diao et al review[105], most of the placebo trials[117, 187, 195-199] in which previous treatments were not permitted or were withdrawn did not observe substantial effects of active drug treatment on major CVD events, CHD, stroke or all-cause deaths within the trial period.

Concerns have been raised around a so called 'legacy effect': that is an irreversible pathological damage due to delaying treatment after a patient reaches a SBP threshold of 140 mmHg Two systematic reviews[185, 186] have been conducted of blood pressure lowering trials with a post-trial follow-up of up to ten years and shown a significantly reduced risk of CVD and all-cause mortality in the participants randomly allocated to active treatment. However, these two reviews included patients with pre-existing cardiovascular disease. Therefore, the 'legacy effect' of delayed drug treatment in individuals with mildly elevated SBP without cardiovascular disease remains uncertain. As there are no trials that addressed this specific question, the aim of this review is to investigate if there are any adverse 'legacy effects from not initiating drug treatment at a systolic BP threshold of 140 mmHg in 'healthy' middle-age adults using post-hoc analyses of existing trials with long-term follow-up.

Methods

Protocol and registration

The review protocol was published in the Journal of Medical Internet Research[200] and can be accessed via https://www.researchprotocols.org/2017/9/e177/. The review was registered in PROSPERO International Prospective Register of Systematic Reviews: CRD42017058414

Criteria for considering studies for this review

Population

Trials including men and non-pregnant women from 30 to 65 years of age, where at least 80% of participants in the trial had mildly elevated BP at baseline (defined as a SBP of 140 – 159 mmHg) and no history of CVD (myocardial infarction, angina pectoris, coronary bypass surgery, coronary angioplasty, stroke, transient ischaemic attack, carotid endarterectomy, surgery for peripheral vascular disease, intermittent claudication or renal failure (creatinine > 1.5 times the upper limit of normal) at baseline were eligible. Where trials included participants different to those of interest (e.g. in secondary prevention populations, in participants with moderately or highly elevated BP or older than 65 years), we attempted to access individual patient data from trial

investigators and subsequently included only participants meeting our criteria in the analyses.

Intervention

The study included all types of BP-lowering drugs, except for some types that have limited clinical use due to the risk of side effects and availability (eg, ganglion blockers, reserpine, rauwolfia).

Comparison

We included studies that used a placebo or untreated control comparator or another active BP lowering treatment where it was possible to determine participants who had previously been taking blood pressure lowering treatment (previous treatment) or no pre-existing treatment (treatment naïve).

Outcomes

The primary outcome of the review was all-cause mortality, with secondary outcome of CVD mortality and CVD events (defined as fatal and non-fatal stroke, fatal and non-fatal CHD, fatal and non-fatal heart failure).

Study design

The current review included randomised controlled trials (RCTs) with at least 1-year post-trial follow-up.

Data sources and searches

We searched Medline via Ovid (1946 to Sept 2018), Embase via Ovid (1974 to Sept 2018) and the Cochrane Register of Controlled Trials (CENTRAL) (Sept 2018). We combined text word and MeSH/Emtree terms related to BP lowering drug agents with hypertension terms and follow-up studies. We used the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (sensitivity and precision maximising 2008 revision) in Medline[201]. No language restrictions were applied. The search strategies are provided in Table appendix 4.1. We modified the search strategy from the published protocol[200] as the planned method identifying trials and then searching for follow-up studies was considered inadequate to identify potentially eligible RCTs.

We searched reference lists of known systematic reviews on post-trial studies of BP lowering drug treatment (Kostis 2010[185] and Hirakawa 2017[186]) or meta-analyses on trials of middle-aged adults with mildly elevated BP[88, 105,

[202, 203]. We contacted corresponding authors of relevant papers regarding any further published or unpublished work.

Study selection

Two reviewers (CH and SS) independently scanned the results of the title and abstract search and any potentially relevant articles were obtained in full text. Two reviewers then screened the full text of potentially relevant articles against the reviews inclusion criteria. Discrepancies were resolved through discussion with a third reviewer

Data extraction

Data extraction were independently performed by two reviewers (CH and SS). If any disagreement arises, two reviewers discussed or consulted with the third reviewer (JD). Generally, the extraction form included details of study characteristics, participant characteristics, interventions and settings, outcome data, type of analysis used in the studies, follow-up years.

Assessment of risk of bias in included studies

Two review authors (CH and SS) independently assessed risk of bias using the Cochrane Risk of bias in non-randomised and /randomised studies of interventions tools [206, 207]. The ALLHAT study was assessed using the tool for non-randomised studies as data from the original randomised trial was reanalysed to compare non-randomised groups (treatment naïve vs previous treatment) based on data collected at trial baseline. Risk of bias assessment in both non-randomised[31,208] and /randomised studies[30, 209] included consideration of four mutual domains: bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported. Risk of bias assessment in non-randomised controlled studies required consideration of three further criteria: bias due to confounding, bias in selection of participants into the study and bias in classification of intervention. For randomised studies, risk of bias assessment also included consideration of bias arising from the randomisation process. For the non-randomised studies, each risk of bias domain was assessed as low, moderate, serious or critical risk of bias with a no information response when insufficient data were reported to permit a judgment. For the randomised studies, each risk of bias domain was

assessed as low, some concerns and high risk of bias. The domain level judgments provide the basis for an overall risk of bias judgment for each study. An assessment of potential publication bias was not performed due to the small number of included studies.

Data analysis

We compared outcomes in the short-term (average 5-year in-trial period) and long-term (an overall period of at least 10 years cumulative in- and post-trial period) between 'delayed treatment' and 'early treatment' groups. The 'early treatment' group included who had been previously treated with blood pressure lowering treatment at trial entry and the 'delayed treatment' group included participants who were treatment naïve using individual patient data from the trial. This approach has been used previously by Nelson et al[188].

Due to the small number of included studies, fixed effect Peto odds ratio (OR) was used to estimate the pooled effects [210,27-29]. As recommended, we also used other methods to test the robustness of the results in sensitivity analyses. Heterogeneity of treatment effects in different trials were tested by the I^2 statistic. Statistical heterogeneity was recorded when the p value of the test of heterogeneity was 0.1 or lower or the I^2 value was 0.5 or greater. In a post-hoc analysis of the ALLHAT trial, the effects of 'no previous treatment' versus 'previous treatment' (PT) for high BP by hazard ratio were estimated using a Cox proportional hazard model. As this analysis was a comparison of non-randomised groups, the two groups were adjusted for an imbalance in baseline characteristics (e.g. age, race, sex, diabetes mellitus, education, body mass index, smoking, aspirin, randomised group, blood pressure, total cholesterol, serum glucose and creatinine), as per Nelson et al in the ANBP2 study[188]. The observed (O), expected event (E) and variance (V) in ALLHAT were estimated from adjusted HR as recommended by Tierney et al [211] and then pooled with the corresponding O, E and V in Oslo and PREVEND-IT. The threshold of a significant effect was set at 0.05.

We conducted a subgroup analysis based on baseline risk of CVD where data were available. Included participants were stratified by the baseline estimated 10-year Framingham risk score (fatal and non-fatal CVD events).

Due to inconsistent thresholds of 10-year Framingham risk score [2, 3], conventional thresholds of lower than 20%, 20-30% and higher than 30% were chosen to stratify participants into low, moderate and high risk groups correspondingly in this study. We estimated the relative risk for all-cause and CVD mortality in each group and tested for difference between the groups. Data synthesis and analyses were run on Review Manager 5 [212]. We extracted data based on intention-to-treat principles.

Sensitivity analysis

An analysis restricted to placebo/untreated controlled RCTs was performed to investigate the impact of the observational study on the pooled outcomes. Different statistical methods were used to check the robustness of the results[27-29].

Results

Result of the searches

The database searches identified 6012 records and three articles were identified from other sources (Figure Appendix 4.1 shows the flowchart of studies). After removal of duplicates 4090 articles were screened. Eighty nine articles were screened in full-text and 3 studies (Oslo, PREVEND-IT and ALLHAT) from 11 articles were included in the review. Aggregate unpublished data from the ALLHAT and individual data of PREVEND-IT trial were provided by the trial investigators.

One trial excluded from the review included participants with mildly elevated diastolic BP (90-115 mmHg): USPHS 1977[204, 205]. Although USPHS did not have a post-trial phase, the trial was followed for up to 10 years. No information on the proportion of participants with mildly elevated systolic BP was reported. Based on the baseline systolic BP148±15 mmHg, it is likely that less than 80% of participants had systolic BP less than 160 mmHg. The intervention was a combination of a diuretic and rauwolfia serpentine that had limited clinical use in current practice because of the risk of side effects and availability. Thus USPHS was excluded in the current systematic review and meta-analysis.

Characteristics of included studies and risk of bias

The review included published data of the Oslo trial, unpublished aggregate data of ALLHAT and individual data of the PREVEND-IT trial. As ALLHAT is a randomised active-controlled trial, we used data based on whether participants had previously been treated with BP lowering agents or not, that is a comparison on a difference in treatment status at baseline between the two groups rather than a randomised comparison. ALLHAT participants were followed for a mean of 4.9 years in the in-trial period and 14 years over the in- and post-trial period. As the original ALLHAT trial [189] reported beneficial effects from BP lowering treatment within the trial period, the majority of participants from all arms of the trials received active treatment in the post-trial phase, so there is likely to be little cross-over between the early treatment and delayed treatment comparison groups. Although some participants in the Oslo trial may have diastolic BP exceeding 110 mmHg, nearly 80% of Oslo participants had systolic BP lower than 160 mmHg, so we included the published data of this trial. Oslo reported 10-year[116] and 40-year[115] follow-up of all-cause mortality and coronary heart disease (CHD) deaths, thus the results of the 40-year study were included in the review. In PREVEND-IT trial, participants were originally randomised either to active treatment (Fosinopril 20 mg) or placebo. The mean follow-up period ranged from 3.3-4.4 years for the in-trial phase and 9.4-10.7 years for the overall period.

The baseline risk for participants in ALLHAT was higher than the other two trials as it included participants with elevated BP and at least one other CVD risk factor (e.g. history of type 2 diabetes, current cigarette smoking, high-density lipoprotein cholesterol of less than 0.91 mmol/L). PREVEND-IT included healthy subjects from general population with persistent microalbuminuria, and the Oslo trial was restricted to men with mildly elevated BP defined as systolic BP 150-179 mmHg and diastolic BP less than 110 mmHg. The median follow-up period ranged from 3.8-5.5 years for the in-trial phase and 9.5-40 years for the overall period. More details on characteristics of included studies were provided in Table appendix 4.2.

The baseline characteristics of the participants included in the review showed no significant differences between study groups in the PREVEND-IT and Oslo trials (Table 4.1). ALLHAT participants had a higher proportion of patients with diabetes and contributed to a higher proportion of participants with early treatment having type 2 DM. Participants with early treatment in the ALLHAT trial were more likely to be black, female, non-smoker and had type 2 DM and had higher estimated 10-year CVD risk scores. These imbalance characteristics were adjusted in multivariable models. Noticeably, Oslo restricted to men only and were likely to have higher systolic BP than other two trials.

Table 4.1.Baseline characteristics of included participants

Characteristics	Delayed			Early		
	ALLHAT	**PREVEND-IT**	**Oslo**	**ALLHAT**	**PREVEND-IT**	**Oslo**
Number of observations, n	509	70	379	3303	79	406
Age (mean ± SD, years)	59.5 ± 2.9	52.3±8.0	45.2±2.8	59.5 ± 2.9	50.3±8.2	45.3±2.9
Black, %	**34.6***	0	NA	**43.6**	1.3	NA
Male, %	**52.8***	64.3	100	**46.3**	65.8	100
Current Smoker, %	**43.8***	32.9	42.5	**34.6**	34.2	40.9
BMI (mean ± SD, kg/m^2)†	**29.9 ± 5.9***	28.1± 4.2	NA	**31.3 ±7.1**	27.7±4.7	NA
Diabetes† (%)	**41.7***	2.9	0	**51.1**	2.5	0
SBPs (mean ± SD, mmHg):	**147± 7***	147± 6	155±8	**146 ± 8**	148±6	156±7
DBPs (mean ± SD, mmHg):	**88±7***	84±8	96±7	**87±7**	85±7	97±7
Fasting Serum Glucose† (mmol/L)	**7.2± 3.5***	5.3±1.4	6.0±0.6	**7.6 ± 3.8**	5.3±1.8	6.0±0.6

Total cholesterol (mmol/L)	5.6 ± 1.1	6.1±1.1	7.1±1.2	5.7 ± 1.2	6.1±0.9	7.1±1.2
HDL-c† (mmol/L)	1.2 ± 0.4	1.0±0.3	NA	1.2 ± 0.4	1.0±0.3	NA
Serum Creatinine† (umol/L)	82.2 ± 27.4	82.4±14.0	96.9±13.7	84.0 ± 27.4	84.8±14.5	97.2±14.0
10-year FRS, mean (SD)	**27.7 ± 12.8***	20±12	NA	**34.2 ± 15.5**	21±16	NA

*: p<0.05. ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial. NA: not available. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, HDL: High Density Lipoprotein cholesterol, FRS: Framingham Risk Score.

Risk of bias (Table 4.2)

We assessed the ALLHAT data to be at serious risk of bias due to residual confounding as a result of the use of post-hoc non-randomised data from the trial, and this resulted in a grading for the overall risk of bias of ALLHAT of 'serious risk'. Although the outcome measurements in the post-trial phase of the PREVEND-IT and Oslo trials were unblinded, the primary outcomes considered in this analysis are generally objective (all-cause and cardiovascular mortality). Thus, the overall risk of bias for PREVEND-IT and Oslo trial was judged as 'Low risk'. Analyses in all three trials were based on the 'Intention to treat' principle since this was appropriate for the research question which related to 'assignment of intervention'. More details on each criterion was presented in Table appendix 4.3

Table 4.2 *Risk of bias*

Risk of bias domain	**ALLHAT 1994**	**PREVEND-IT 1998**	**Oslo 1972**
Bias arising from the randomisation process	NA	Low risk	Low risk
Bias due to deviations from intended interventions	NI	Low risk	Low risk
Bias due to missing outcomes	NI	Low risk	Low risk
Bias in measurement of the outcomes	Low risk	Low risk	Low risk
Bias in selection of the reported results	NA	Low risk	Low risk

Risk of bias domain	**ALLHAT 1994**	**PREVEND-IT 1998**	**Oslo 1972**
Bias in selection of participants into the study	Low	NA	NA
Bias in classification of intervention	Moderate risk	NA	NA
Bias due to confounding	Serious risk	NA	NA
Overall risk of bias	Serious risk	Low	Low

NA: not applicable, NI: no information, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial.

Short- and long-term all-cause and CVD mortality

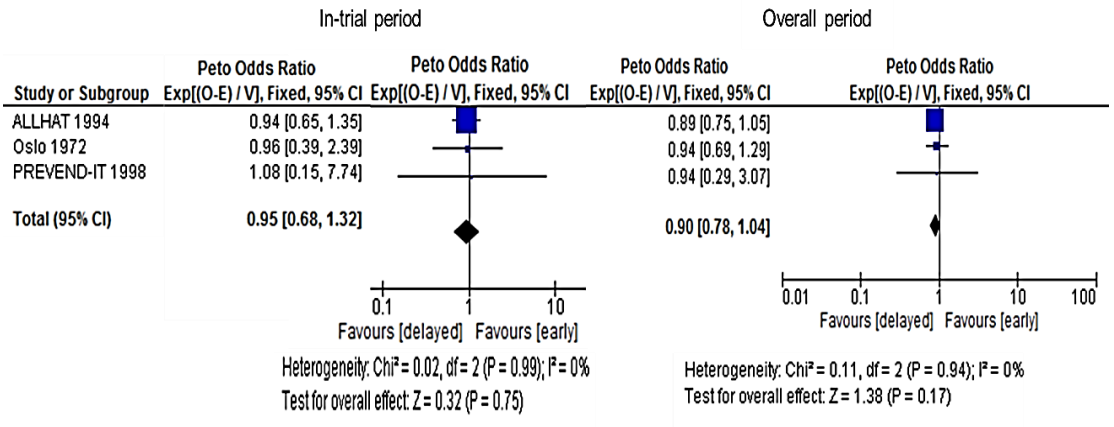
The analyses on short- and long-term all-cause mortality and short-term CVD mortality included 4746 participants from three trials, with 80% originating from the ALLHAT trial. As Oslo separately reported aggregate data of CHD and stroke, Oslo was excluded in the analysis of long-term CVD mortality, leaving 3961 participants in the analysis. There were 301 total deaths, in which 102 deaths due to CVD were recorded in the in-trial period and increased to 1871 total deaths and 312 CVD deaths during the post-trial period (Table appendix 4.5).

We observed no statistically significant difference in all-cause mortality in either the short- or long-term (short-term OR 0.95, 95%CI 0.68-1.32; long-term OR 0.90, 95%CI 0.78-1.04) for those with delayed BP lowering treatment relative to those with earlier treatment. Similarly, no difference was found for CVD mortality (short-term OR 0.90, 95%CI 0.51-1.59; long-term OR 0.79, 95% CI 0.55-1.14). (Figure 4.1)

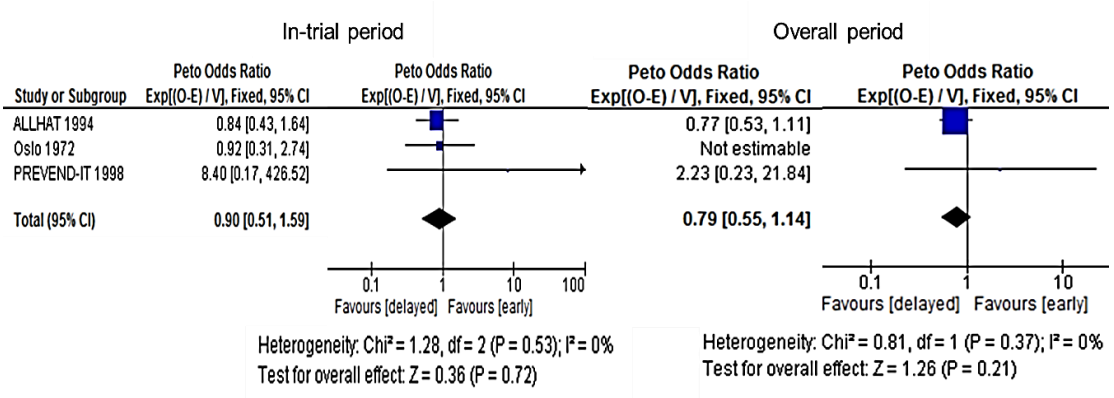
Major CVD events

Two trials (Oslo and PREVEND-IT) including 934 participants contributed to the analysis of major CVD events in the short-term, with 69 events recorded

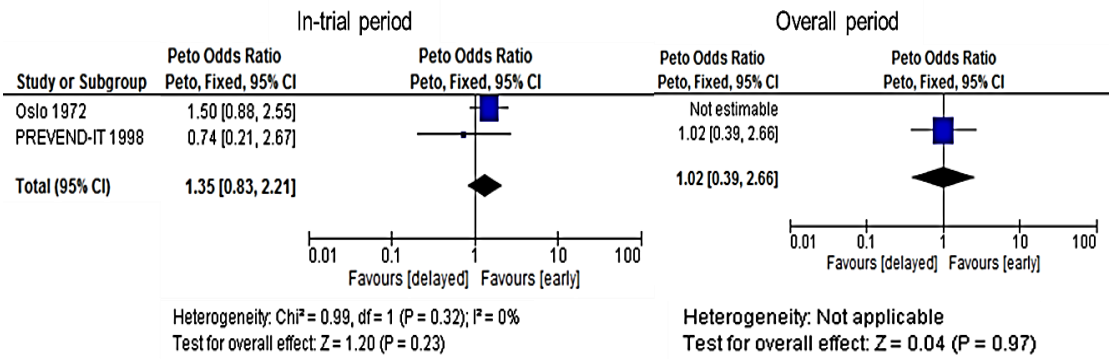
in the in-trial phase of Oslo and PREVEND-IT trial (Table appendix 4.5). However only PREVEND-IT (149 participants, 19 events) recorded long-term outcomes. Delayed' drug treatment was associated with a modest, though not statistically significant, increased risk of major CVD events with OR 1.35 (0.83-2.21) for the short-term phase. There was no evidence for long-term effects in PREVEND-IT with OR 1.02 (0.39-2.66) (Figure 4.1)



(A) All-cause mortality during the in-trial and overall follow-up



(B) Cardiovascular disease death during the in-trial and overall follow-up



(C) Major cardiovascular disease during the in-trial and overall follow-up.

Figure 4.1. Forest plot for outcomes during the in-trial and overall follow-up.

CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial.

Subgroup analysis by 10-year Framingham risk score (Figure 4.2 and Figure 4.3)

Data were available to stratify participants in ALLHAT and PREVEND-IT into low, moderate and high risk of CVD. More than half of the included participants were in the high risk group, primarily due to the inclusion criteria of the ALLHAT study. The effects of delayed BP lowering drug treatment were consistent among the three groups (p=0.46 and p=0.79 for the test of subgroup differences in overall all-cause and CVD mortality respectively)

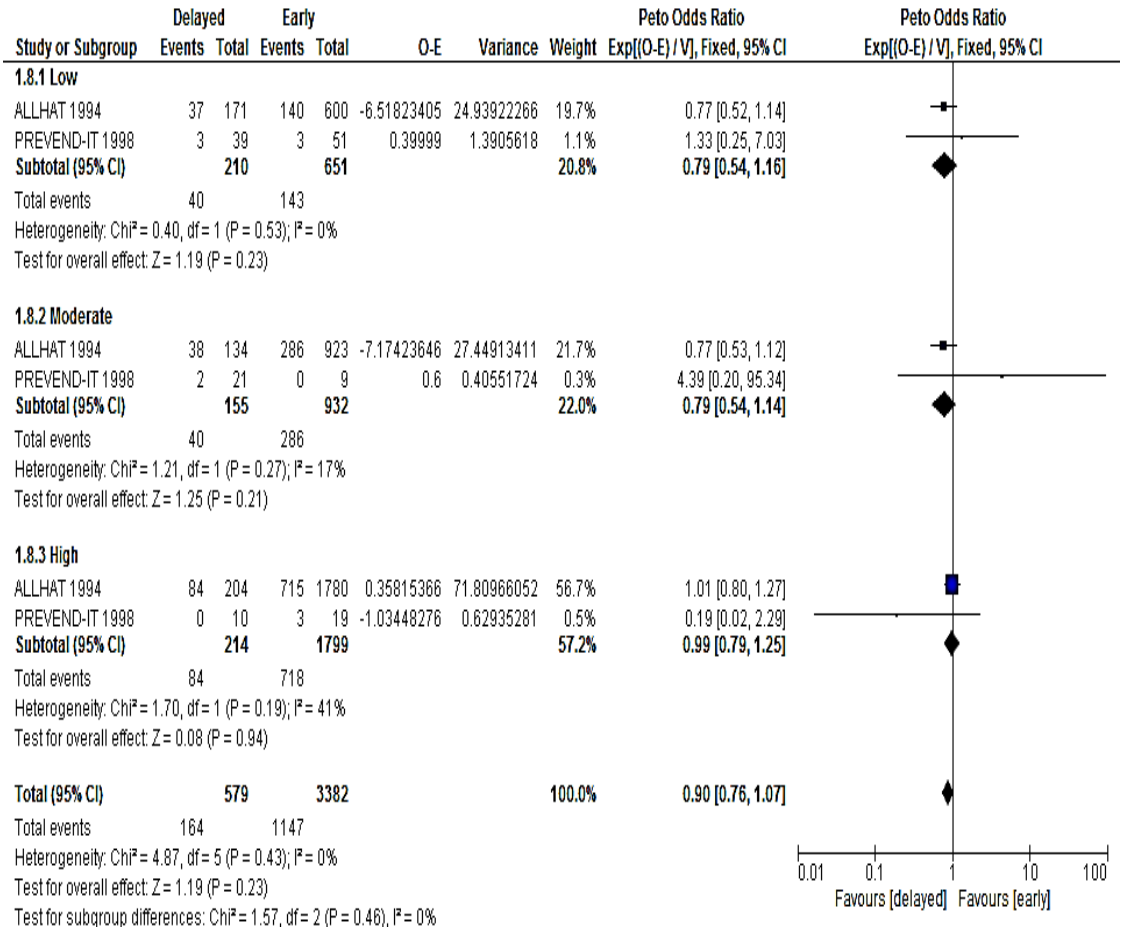


Figure 4.2. Forest plot for overall all-cause mortality in subgroup by 10-year Framingham risk score.

CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial.

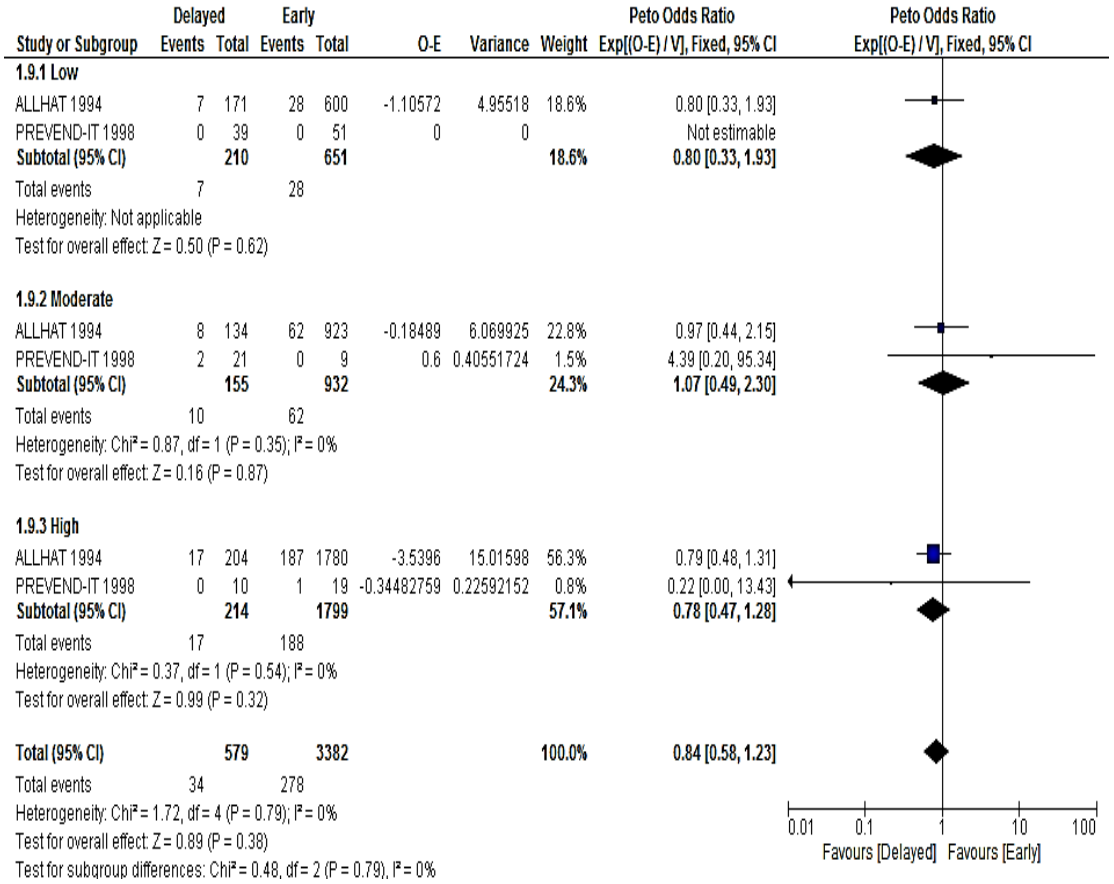


Figure 4.3. Forest plot for overall CVD mortality in subgroup by 10-year Framingham risk score.

CI: Confidence interval, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial.

Sensitivity analysis

Using different methods (DerSimonian-Laird between-study variance estimator and Wald-type confidence intervals , DerSimonian-Laird between-study variance estimator and Hartung-Knapp-Sidik-Jonkman adjusted confidence intervals, Paule-Mandel between-study variance estimator and Hartung-Knapp-Sidik-Jonkman confidence intervals) to pool the aggregate

data did not change the main findings in all-cause and CVD mortality as presented in Table appendix 4.6.

An analysis restricted to the data from the randomised trials only (PREVEND-IT and Oslo), were similar to the main analyses, with no statistically significant difference in for short-term all-cause mortality (OR 0.99, 95% CI 0.43-2.27) or long-term all-cause mortality (OR 0.94, 95% CI 0.70-1.28) or short- or long-term CVD mortality (short-term OR 1.26, 95% CI 0.42 - 3.76; long-term OR 2.23, 95%CI 0.23-21.84) (Table appendix 4.7).

A sensitivity analysis adjusting for baseline differences, showed no substantial difference between the adjusted and crude hazard ratio for any outcome (Table appendix 4.8).

Discussion

The present systematic review and meta-analysis of studies with extended post-trial phase recorded no significant different in risk of all-cause and CVD mortality for participants with 'delayed' drug treatment at a systolic BP threshold of 140 mmHg in middle-aged adults even when the follow-up was extended for more than ten years. Due to the small number of events in the in-trial period, subgroup analyses were performed only for long-term all-cause and CVD mortality. No heterogeneity of 'delayed' treatment effects was found across the three risk subgroups.

Our findings are similar to two earlier systematic reviews in middle-aged adults without previous CVD[213] and in middle-aged adults both with and without previous CVD [202]. Trials in these reviews had follow-ups of approximately five years, except for the USPHS study[205]. The USPHS was followed for 7-10 years and recorded a non-significant association between 'early' treatment and reduced all-cause mortality with a RR 0.51 (0.09-2.74). Results from USPHS may not be considered relevant to current populations, however, as this trial used rauwolfia, which is no longer recommended treatment. Similar to our short-term results, the SHEP[119] and Syst-Eur[123] trials did not record any substantial benefits of 'early' treatment for all-cause or CVD mortality after an in-trial follow-up of five and two years respectively. However, the effects on CVD mortality became statically significant with a HR 0.86 (0.76-0.97) when the

SHEP trial was extended to 14 years[120] and such a 'legacy effect' remained significant at the 22-year follow-up[214]. The mortality effects in Syst-Eur remained non-statistically significant after a total follow-up of 6 years[215], indicating that a longer time for follow-up is required to observe significant 'delayed benefits'. The SHEP and Syst-Eur trials had an actual 'placebo' arm when participants experienced 'placebo' run-in or withdrawal phase, however these trials were aimed at the elderly with much higher BP value of 160 mmHg or over compared to our included participants.

Benefits of 'active treatment' or harms of 'no treatment' may require longer than ten years to become evident, particularly on mortality outcomes in middle-aged adults with mildly elevated BP who are likely to be at low CVD risk. This is the group that where treatment with blood pressure lowering medication is not clearly of benefit. We have attempted in this review to determine if treatment can safely be delayed in this treatment group. In this review, the average Framingham risk score was >20%, and so is higher than the low risk patients we would consider where treatment could be delayed. Even in this review, however, no clear evidence of early treatment was observed. The included ALLHAT and Oslo trial[115] were extended to 14 and 40 years respectively, with no substantial adverse 'legacy effect' on all-cause or CVD mortality of delayed treatment observed, and we observed consistent results across the low, moderate and high CVD risk subgroups.

Strengths and limitation

This is the first study to systematically review the medical evidence to determine if delaying BP lowering treatment for middle-aged adults with a systolic BP between 140 and 159 mmHg results in an increase in all-cause or cardiovascular mortality in the short or long term.

In spite of vigorous efforts in accessing individual data to identify eligible participants, only three studies with 4746 participants could be included in the current review. Given the much larger sample size of ALLHAT trial, the overall results were heavily influenced by the results of the ALLHAT trial. In the ALLHAT trial, information on how long before the start of the trial participants had been on BP lowering treatment was not collected and even if it was, we

could not truly know how long someone was hypertensive before it was noted. Also, the study design of ALLHAT (post-hoc observational) is different from the other two randomised controlled trials (PREVEND-IT and Oslo). However, in sensitivity analysis on short- and long-term all-cause mortality, the results of analyses excluding the ALLHAT trial were generally consistent with the overall results.

This review did not examine CHD and stroke mortality separately. Given the small number of studies and the potential for CHD and stroke to be affected by different classes of BP lowering medication [40, 74], we were only able to assess overall and total CVD mortality.

The three included trials lacked BP lowering drug treatment information in the post-trial phase, except that an equal percentage of participants receiving drug therapy were reported in PREVEND-IT and Oslo trial. Given the 'positive' findings of the original ALLHAT trial, we believe it is likely that a substantial proportion of both arms of the trial would have used BP lowering therapy after the trial period.

We used the Peto method for meta-analysis because of the small number of included studies. While it is true that the Peto method is open to bias when including studies with imbalance in the comparison groups, this only becomes apparent in combination with a large treatment effect[210]. Also, different statistical methods provided similar pooled effects as provided in Table appendix 4.6.

Due to the above limitations, the results should be carefully interpreted. 'Legacy effects' in low risk population with mild hypertension should be investigated in further studies, however a long-term trial in such a low risk population is not likely to be feasible due to time commitment, money and other practical issues. A large observational study with the use of electronic health records should be considered.

One of the barriers to adopting the absolute risk approach for decisions regarding BP lowering treatment is the concern that early treatment of mildly elevated BP is necessary to prevent pathological changes that result in CVD events. The current systematic review and meta-analysis showed no evidence

of an association between delayed treatment and CVD or death in middle-aged adults at a systolic BP threshold of 140 mmHg or over at any CVD risk subgroup. This study contributes to an area of major concern raised by many clinicians that early treatment of mildly elevated BP is necessary to prevent CVD events.

Postscript

The findings in this study and previous chapters manifested the non-significant benefits or harms of delaying or untreating BP lowering drug treatment in low or moderate CVD risk, particularly middle-aged adults with mildly elevated BP. Similarly, the next chapter will investigate the effect of lipid lowering drug treatment versus no treatment in the elderly across the CVD risk subgroup.

Appendix

Table appendix 4.1 Search strategy

MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Date: 24 Sept 2018

---

1 exp Antihypertensive Agents/ (259590)

2 (antihypertensive$ adj (agent$ or drug)).tw. (11275)

3 exp Thiazides/ (16149)

4 exp Sodium Chloride Symporter Inhibitors/ (14961)

5 exp Sodium Potassium Chloride Symporter Inhibitors/ (14368)

6 ((ceiling or loop) adj diuretic?).tw. (2922)

7 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (36600)

8 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (2551)

9 exp Angiotensin-Converting Enzyme Inhibitors/ (44128)

10 angiotensin converting enzyme inhibit$.tw. (19920)

11 (ace adj2 inhibit$).tw. (19752)

12 acei.tw. (3311)

13 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or

trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (28628)

14 exp Angiotensin Receptor Antagonists/ (21660)

15 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (13192)

16 arb?.tw. (6139)

17 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw. (17067)

18 exp Calcium Channel Blockers/ (83927)

19 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (65375)

20 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (41141)

21 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (16483)

22 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine

or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (21355)

23 exp Hydralazine/ (4913)

24 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (4755)

25 exp Adrenergic beta-Antagonists/ (87205)

26 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw. (67238)

27 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (104465)

28 exp Adrenergic alpha-Antagonists/ (52071)

29 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (15051)

30 (adrenergic adj2 (alpha or antagonist?)).tw. (20736)

31 ((adrenergic or alpha or receptor?) adj2 block$).tw. (61684)

32 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (560290)

33 exp Hypertension/ (252124)

34 hypertens$.tw. (405123)

35 ((high or elevat$ or rais$) adj2 blood pressure).tw. (28379)

36 exp Cardiovascular Diseases/pc [Prevention & Control] (187726)

37 33 or 34 or 35 or 36 (636841)

38 randomized controlled trial.pt. (497432)

39 controlled clinical trial.pt. (99269)

40 randomized.ab. (434110)

41 placebo.ab. (202971)

42 clinical trials as topic/ (195636)

43 randomly.ab. (299164)

44 trial.ti. (196020)

45 38 or 39 or 40 or 41 or 42 or 43 or 44 (1212939)

46 animals/ not (humans/ and animals/) (4646041)

47 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (916617)

48 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti. (17005)

49 45 not (46 or 47 or 48) (1081328)

50 exp Follow-Up Studies/ (627771)

51 (1$ year follow up or 2$ year follow up or 3$ year follow up or 4$ year follow up or 5$ year follow up or 6$ year follow up or 7$ year follow up or 8$ year follow up or 9$ year follow up).tw. (56294)

52 follow$.tw. (3159033)

53 (post trial or posttrial or post-trial or after trial or long term or longterm or long-term or extension or extended or observation$ or passive or longitudinal).tw. (2075721)

54 52 and 53 (506270)

55 50 or 51 or 54 (1049694)

56 32 and 37 and 49 and 55 (2681)

57 (legacy adj effec$).tw. (183)

58 56 or 57 (3038)

Appendix 2. EMBASE search strategy

Database: Ovid Embase <1974 to 2017>

Search Date: 24 Sept 2018

---

1 exp Antihypertensive Agents/ (648405)

2 (antihypertensive$ adj (agent$ or drug)).tw. (14296)

3 exp thiazide diuretic agent/ (52373)

4 exp loop diuretic agent/ (67171)

5 ((ceiling or loop) adj diuretic?).tw. (4074)

6 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (42735)

7 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (3789)

8 exp dipeptidyl carboxypeptidase inhibitor/ (159353)

9 angiotensin converting enzyme inhibit$.tw. (23320)

10 (ace adj2 inhibit$).tw. (27469)

11 acei.tw. (6301)

12 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril$ or perindopril$ or pivopril or quinapril$ or ramipril$ or rentiapril or saralasin or s nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utibapril$ or zabicipril$ or zofenopril$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (37069)

13 exp Angiotensin Receptor Antagonists/ (79298)

14 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (18175)

15 arb?.tw. (11361)

16 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw. (25409)

17 exp calcium channel blocking agent/ (208343)

18 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (79546)

19 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (47871)

20 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (28741)

21 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (46100)

22 exp Hydralazine/ (18331)

23 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (6395)

24 exp beta adrenergic receptor blocking agent/ (273269)

25 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or

metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw. (80953)

26 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (119505)

27 exp alpha adrenergic receptor blocking agent/ (131347)

28 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (16958)

29 (adrenergic adj2 (alpha or antagonist?)).tw. (18457)

30 ((adrenergic or alpha or receptor?) adj2 block$).tw. (73216)

31 or/1-30 (979528)

32 exp Hypertension/ (633764)

33 hypertens$.tw. (553609)

34 ((high or elevat$ or rais$) adj2 blood pressure).tw. (37199)

35 32 or 33 or 34 (817103)

36 Random:.tw. (1253377)

37 Placebo:.mp. (408004)

38 Double-blind:.tw. (183950)

39 36 or 37 or 38 (1496703)

40 follow*.tw. (4064909)

41 (post trial or posttrial or post-trial or after trial or longterm or long term or long-term or extension or extended or observation* or passive or longitudinal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (2664945)

42 40 and 41 (726994)

43 31 and 35 and 39 and 42 (1728)

44 (legacy adj effect$).tw. (191)

45 43 or 44 (2021)

CENTRAL search strategy

Database: Cochrane Central Register of Controlled Trials on Wiley

Search Date: 23 October 2017

---

1 MeSH descriptor: [1] explode all trees (7669)

2 (antihypertensive* near (agent* or drug)):ti,ab (2327)

3 MeSH descriptor: [Thiazides] explode all trees (2350)

4 MeSH descriptor: [Sodium Chloride Symporter Inhibitors] explode all trees (368)

5 MeSH descriptor: [Sodium Potassium Chloride Symporter Inhibitors] explode all trees (49)

6 ((ceiling or loop) next diuretic*):ti,ab (417)

7 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*):ti,ab (5283)

8 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide):ti,ab (974)

9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 (13928)

10 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees (3961)

11 angiotensin converting enzyme inhibit*:ti,ab (5281)

12 (ace near/2 inhibit*):ti,ab (3222)

13 acei:ti,ab (697)

14 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril):ti,ab (7926)

15 #10 or #11 or #12 or #13 or #14 (11126)

16 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees (2005)

17 (angiotensin near/3 (receptor antagon* or receptor block*)):ti,ab (2387)

18 arb*:ti,ab (2739)

19 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten):ti,ab (5211)

20 #16 or #17 or #18 or #19 (8123)

21 MeSH descriptor: [Calcium Channel Blockers] explode all trees (2871)

22 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM):ti,ab (11734)

23 (calcium near/2 (antagonist* or block* or inhibit*)):ti,ab (4515)

24 #21 or #22 or #23 (13375)

25 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa):ti,ab (596)

26 (clonidine or adesipress or arkamin or caprysin or catapres* or catasan or chlofazolin or chlophazolin or clinidine or clofelin* or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin* or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets):ti,ab,kw (3423)

27 MeSH descriptor: [Hydralazine] explode all trees (309)

28 (hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat):ti,ab (450)

29 #25 or #26 or #27 or #28 (4463)

30 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees (4506)

31 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or

hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol):ti,ab (14371)

32 (beta near/2 (adrenergic* or antagonist* or block* or receptor*)):ti,ab (9274)

33 #30 or #31 or #32 (18895)

34 MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees (1215)

35 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin):ti,ab (2223)

36 (adrenergic near/2 (alpha or antagonist*)):ti,ab (1068)

37 ((adrenergic or alpha or receptor*) near/2 block*):ti,ab (6598)

38 #34 or #35 or #36 or #37 (9280)

39 #9 or #15 or #20 or #24 or #29 or #33 or #38 (54477)

40 MeSH descriptor: [Hypertension] explode all trees (15677)

41 hypertens*:ti,ab (37742)

42 ((high or elevat* or rais*) near/2 blood pressure):ti,ab (2392)

43 MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Prevention & control - PC] (16513)

44 #40 or #41 or #42 or #43 (55008)

45 #39 and #44 (20752)

46 MeSH descriptor: [Follow-Up Studies] explode all trees (54281)

47 follow*:ti,ab (269231)

48 ("post trial" or posttrial or post-trial or "after trial" or "long term" or longterm or long-term or extension or extended or passive or longitudinal):ti,ab (92679)

49 #47 and #48 (40334)

50 (1* next year next "follow up"):ti,ab or (2* next year next "follow up"):ti,ab or (3* next year next "follow up"):ti,ab or (4* next year next "follow up"):ti,ab or (5* next year next "follow up"):ti,ab or (6* next year next "follow up"):ti,ab or (7* next year next "follow up"):ti,ab or (8* next year next "follow up"):ti,ab or (9* next year next "follow up"):ti,ab (12590)

51 #49 or #50 (48897)

52 #45 and #51 (862)

53 (legacy near effect*):ti,ab (15)

54 #52 or #53 (953)

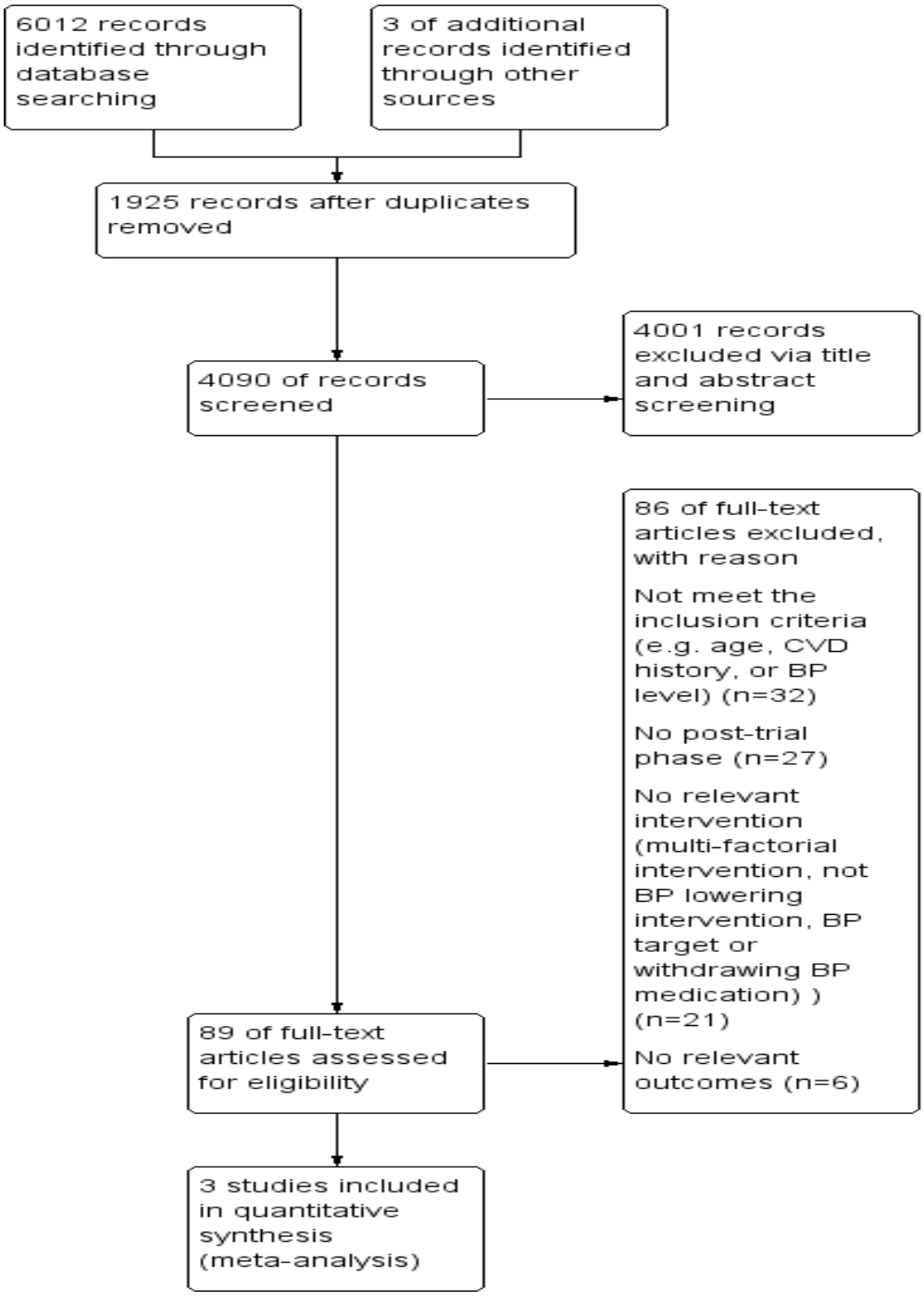


Figure appendix 4.1. Study flow diagram

Table appendix 4.2. Characteristics of included studies

Trials	Trial entry criteria	In-trial comparison	Comparison in this review	Number of participants in this analysis* / in-trial sample size	Follow-up In-trial (Mean years)	Follow-up Overall	% Receiving BP drug treatment in post-trial phase	Sources of mortality outcomes in post-trial phase
ALLHAT	Untreated SBP<180 or treated SBP <160 mmHg +≥ 1 CVD risk factors.	Chlorthalidone 12.5 to 25 mg/d vs amlodipine 2.5 to 10 mg/d vs lisinopril 10 to 40mg/d	'previous treatment' (early) vs 'treatment naïve' (delayed)	3872/ 33357	4.9	**1**4	Not reported.	National Death Index, Social Security Administration databases and confirmatory death certificate
PREVEND-IT	BP < 160/100 mmHg, no BP lowering medication + persistent albuminuria.	Fosinopril 20 mg vs placebo	Fosinopril 20 mg (early) vs placebo (delayed)	149/864	4	10	Reported "rate of ACE inhibitor…use remained similar in all former randomised groups"	Municipal register and Dutch Central Bureau of Statistics
Oslo	Men, systolic BP 150-179 mmHg and diastolic BP	Hydrochlorothiazide 50 mg vs untreated	Hydrochlorothiazide 50 mg (early) vs untreated (delayed)	785/785	5.5	40	Not reported	Statistics Norway

Trials	Trial entry criteria	In-trial comparison	Comparison in this review	Number of participants in this analysis* / in-trial sample size	Follow-up In-trial (Mean years)	Follow-up Overall	% Receiving BP drug treatment in post-trial phase	Sources of mortality outcomes in post-trial phase
	< 110 mmHg.	(propranolol or methyldopa were added to regimen if required)						

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial. * Included participants referred to those who were at middle-age, had no history of CVD and had systolic BP ranging 140-159 mmHg.

Table appendix 4.3. Risk of bias in included studies

ALLHAT

Risk of bias

Bias	Reviewer' judgement	Support for judgement
Bias due to confounding	Serious risk	In this review, data from the randomised trial comparing active treatments was re-analysed and outcomes for participants were compared based on participants treatment status (‘treatment naïve’ or ‘previously treated’ with blood pressure lowering medications) at entry to the original trial. Although treatment effects in this re-analysis were adjusted for the baseline characteristics age, gender, race, diabetes mellitus, education BMI, smoking, aspirin, randomisation group, systolic and diastolic BP, total cholesterol and glucose, some important residual or unmeasured confounders may be present such as dose and duration of previous treatment, the duration of elevated BP or subclinical vascular damage.
Bias in selection of participants into the study	Low risk	This analysis included participants in the original trial who did not have CVD at trial entry. Selection into the analysis was not based on participant characteristics observed after the start of the intervention.

Bias	Reviewer' judgement	Support for judgement
Bias in classification of intervention	Moderate risk	For this review data from the original trial which compared active blood pressure lowering treatment groups was reanalysed and the outcomes for participants who were ‘treatment naïve’ and ‘previously treated’ at entry into the original trial are compared. Information on treatment received at trial enrolment would have been obtained at two pre-randomisation visits and/or by chart review at clinical sites. The accuracy of recording of treatment status is uncertain and misclassification of participants to the treatment naïve and previous treatment comparison groups is possible.
Bias due to deviations from intended interventions	No Information	There is no information about the care provided to ‘treatment naïve’ and ‘previous treatment’ groups beyond the assigned in-trial interventions.
Bias due to missing data	No Information	The analysis only includes participants who have post-trial follow up outcome data. The amount of missing data is not known and whether there were differences in missing data between the treatment naïve and previous treatment groups is unknown.

Bias	Reviewer' judgement	Support for judgement
Bias in measurement of outcomes	Low risk	Outcomes in the original trial were documented by a checklist completed at follow-up visits supplemented by death certificates and hospital discharge summaries. Mortality was the primary endpoint. Participants and care providers were not blind to treatment allocation. Outcomes in the post-trial period were ascertained from the National Death Index using social security number, name, sex and date of birth as matching criteria. Whether outcome measurement was influenced by knowledge of previous treatment or treatment naivety at baseline in the original trial is not known. Mortality is objective so not likely to be bias in measurement.
Bias in selection of the reported result	Low risk	The review outcomes were unpublished and obtained by contacted with the correspondence author.
Overall risk of bias	Serious risk	The study is judged to be a serious risk of bias due to the potential for bias from confounding and bias in classification of the (post hoc) ‘intervention’.

PREVEND-IT

Risk of bias

Bias	Reviewer' judgement	Support for judgement
Bias arising from the randomization process (random sequence generation, allocation concealment)	Low risk	The allocation sequence was random: "Randomisation was performed in blocks of 20 based on a computer generated randomization list by the pharmacy of Academic Hospital Groningen,…" There is no information on whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. However, baseline characteristics in the drug treatment and control group are similar.
Bias due to deviations from intended interventions	Low risk	Participants, carers and personnel are likely to be unaware of intervention group: "Subjects are randomised to fosinopril 20 mg or matching placebo…". (Diercks et al 2000). Participants appear to have been analysed according to the intervention received for the primary study endpoint.

Bias	Reviewer' judgement	Support for judgement
Bias due to missing outcome data (intrial and post trial period)	Low risk	Data on the primary outcome appears to be available for all randomised participants. “Every surviving participant had a final visit 3 months after the end of the active trial period” (Brouwers et al 2011) and Table 5 in Asselbergs. During the post-trial follow \-up only “2 subjects (0.2%) were lost to follow-up”
Bias in measurement of the outcomes	Low risk	Outcome assessors were not aware of intervention assignment. The primary endpoint in the in-trial period was the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity. “An independent end-point committee reviewed all endpoints. The members of this end-point committee had no knowledge of the subject’s treatment assignment”. For the post -trial period The composite primary end point was “similar to the active trial”. Of the surviving participants at the end of the in-trial period data outcome data was obtained from clinic visits, personal communication and electronic hospital files. “Data on

Bias	Reviewer' judgement	Support for judgement
		mortality was retrieved from the municipal register….” “The independent end point committee of the active trial period reviewed all end points, and the members had no knowledge of subject’s treatment assignments”. (Brouwers 2011)
Bias in selection of the reported results	Low risk	Reported outcome data not selected on the basis of results from multiple outcome measurements or multiple analysis of the data
Overall risk of bias	Low risk	

Oslo

Risk of bias

Bias	Reviewer' judgement	Support for judgement
Bias arising from the randomization process (random	Low	The allocation sequence was random: “The randomisation was performed by a “random number table,”…”

Bias	Reviewer' judgement	Support for judgement
sequence generation, allocation concealment)		There is no information on whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. However, baseline characteristics in the drug treatment and control group are similar.
Bias due to deviations from intended interventions (effect of assignment to intervention)	Low	During the in-trial period participants and clinicians were aware of treatment allocation: “The control subjects did not receive a placebo.”. Deviations from the intended intervention were present: drug treatment was started in the control group when a specified blood pressure threshold was reached. In the active treatment group additional or different blood pressure lowering treatments may have been used if the specified systolic blood pressure threshold was not achieved or if there were side effects. though 17% of the control group commenced blood pressure lowering therapy These deviations reflect usual practice. Participants were analysed according to the group to which they were randomised.

Bias	Reviewer' judgement	Support for judgement
Bias due to missing outcome data (short- and long-term outcomes)	Low risk	At the end of the intrial period 1.7% of participants did not attend for regular examinations but answered a mailed questionnaire (and provided outcome data) at the end of the study period. Data on mortality at long term followup were obtained from “Statistics Norway”. Data on mortality at long term follow up are available for all participants randomised in the original trial (406 in the treatment group and 379 in the control group)(Table 3 of Holme et al 2015).
Bias in measurement of the outcome	Low risk	The outcomes reported at the end of the intrial period included total mortality, cardiovascular mortality, coronary and cerebrovascular events. “The incidence of cardiovascular disease was based on hospital records”. Possible nonfatal cerebrovascular events were evaluated by a diagnostic board with diagnostic criteria in accordance with WHO recommendations. Coronary events were evaluated by a “blind” diagnostic board of two independent cardiologists based on established criteria. The assessment of the outcome of total mortality is not likely to be influenced by knowledge of the intervention

Bias	Reviewer' judgement	Support for judgement
		received. Assessment of coronary events requires some judgment but this was performed by individuals blind to intervention status. The outcomes reported at long term follow up include total mortality and mortality at first MI. This data was obtained from “Statistics Norway”. Observers reporting mortality during the post-trial period are unlikely to be aware of in-trial allocation.
Bias in selection of the reported results.	Low risk	It is not possible to tell whether all reported results correspond with intended outcome measurements, however, outcomes cannot be measured in multiple ways (meaning no opportunity to select from multiple measures) and there is only one way the outcome domain can be analysed.
Overall risk of bias	Low	

Table appendix 4.4. Excluded studies and main reasons for exclusion

Trials (year)	Main reason for exclusion
VA-II 1970[216, 217]	Double blind, randomised placebo controlled trial with no post-trial phase in men with mildly elevated diastolic BP (90-114 mmHg). Follow-up: 3.7 years.
VA-NHLBI 1977[218, 219]	Double blind, randomised placebo controlled trial with no post-trial phase in middle-aged participants with mildly elevated diastolic BP (90-114 mmHg). Follow-up: 3.7 years.
USPHS 1977[204, 205]	Double blind, randomised placebo-controlled trial with no post-trial phase in middle-aged participants with mildly elevated diastolic BP (90-115 mmHg). However the in-trial follow-up was 7-10 years. Baseline BP 148±15 mmHg, thus less than 80% of participants had mildly elevated BP. The intervention was a combination of a diuretic and rauwolfia serpentine that have limited clinical use because of the risk of side effects and availability.
MRC-TMH 1985[220, 221]	Single blind, randomised placebo controlled trial with post-trial phase in middle aged participants with mildly elevated diastolic BP. Post-trial random allocation to continued medication or stopped medication.
SOLVD-Prevention 1992[222, 223]	Double blind, randomised placebo controlled trial with post-trial phase in participants with asymptomatic left ventricular dysfunction. Previous BP lowering drug treatment were continued on top of the randomised regimens. Control group included non-specific antihypertensive therapy. There was no placebo/untreated/treatment naive group.
TOMHS 1995[224]	Double blind, randomised placebo controlled trial with no post-trial phase in participants with mildly elevated diastolic BP (<100 mmHg). Follow-up: 4 years.

Trials (year)	Main reason for exclusion
HOPE 2000 [225-227]	Double blind, randomised placebo-controlled trial with post-trial phase in participants aged > 55 years with history of CVD or diabetes and at least one other CVD risk factors. Previous BP lowering drug treatment were continued on top of the randomised regimens. Control group included non-specific antihypertensive therapy. There was no placebo/untreated/treatment naive group.
AASK 2002[228-230]	Single blind randomised active controlled trial with post-trial phase in African American with hypertensive renal disease. There was no placebo/untreated/treatment naive group.
Benedict 2004[231-233]	Double blind, randomised placebo controlled trial with post-trial phase in participants aged ≥ 40 years with type 2 diabetes mellitus. Previous BP lowering drug treatment were continued on top of the randomised regimens. Control group included non-specific antihypertensive therapy. There was no placebo/untreated/treatment naive group.
ADVANCE 2007[234-238]	Double blind, randomised placebo controlled trial with post-trial phase in participants aged > 55 years with type 2 diabetes mellitus and at least one other CVD risk factors. However, previous BP lowering drug treatment were continued on top of the randomised regimens. Control group included non-specific antihypertensive therapy. There was no placebo/untreated/treatment naive group.
CASE-J 2008[239-242]	Single blind randomised active controlled trial with post-trial phase. This trial recruited only those in the age range of interest (45-65) whose SBP was >=160mmHg.
UKPDS 39 2008[243]	Randomised active controlled trial with post-trial phase in participants with type 2 diabetes mellitus. There was no placebo/untreated/treatment naive group.

VA: The Veterans Administration, VA-NHLBI: The Veterans Administration-National Heart, Lung, and Blood Institute Study Group, USPHS: The United States Public Health Service Hospitals Intervention Trial, MRC-TMH: The Medical Research Council trial of treatment of mild hypertension, SOLVD-Prevention: The Studies of Left

Ventricular Dysfunction, TOMHS: Treatment Of Mild Hypertension Study, HOPE: Heart Outcome Prevention Evaluation, AASK: The African American Study of Kidney Disease and Hypertension, Benedict: The Bergamo Nephrologic Diabetes Complication Trial, ADVANCE: The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, CASE-J: Candesartan Antihypertensive Survival Evaluation in Japan, UKPDS: The UK Prospective Diabetes Study.

Table appendix 4.5 Number of events and participant numbers in this review versus total number in the trials.

Events	Delayed		Early	
	No. of events	N	No. of events	N
Short-term all-cause mortality				
ALLHAT	34	509	244	3303
Oslo	9	379	10	406
PREVEND	2	70	2	79
Long-term all-cause mortality				
ALLHAT	159	509	1141	3303
Oslo	272	379	296	406
PREVEND	5	70	6	79
Short-term CVD mortality				
ALLHAT	10	509	79	3303
Oslo	6	379	6	406
PREVEND	1	70	0	79
Long-term CVD mortality				
ALLHAT	32	509	277	3303
Oslo	NR	379	NR	406
PREVEND	2	70	1	79
Short-term major CVD events				
ALLHAT	NR	509	NR	3303
Oslo	34	379	25	406
PREVEND	4	70	6	79
Long-term major CVD events				
ALLHAT	NR	509	NR	3303
Oslo	NR	379	NR	406
PREVEND	9	70	10	79

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial, NR: Not Reported.

Table appendix 4.6 Estimation of effects of delayed b lowering drug using different statistical methods

Methods	Delayed vs Early
Short-term all-cause mortality	
HKSJ, RE (k=3)	RR 0.95 (0.86-1.05), I^2=0.0% (0.0%;0.0%)
DLRE, RE (k=3)	RR 0.94 (0.0.65-1.36), I^2=0.0% (0.0%;0.0%)
PMHK, RE (k=3)	RR 0.95 (0.86-1.05), I^2=0.0% (0.0%;0.0%)
Long-term all-cause mortality	
HKSJ, RE, (main analysis) (k=3)	RR 0.96 (0.85-1.09), I^2=0.0% (0.0%;82.7%)
DLRE, RE (k=3)	RR 0.96 (0.89-1.04)), I^2=0.0% (0.0%;82.7%)
PMHK, RE (k=3)	RR 0.96 (0.85-1.09), I^2=0.0% (0.0%;82.7%)
Short-term CVD mortality	
HKSJ, RE (k=3)	RR 0.90 (0.43-1.87)), I^2=0.0% (0.0%;70.5%)
DLRE, RE (k=3)	RR 0.90 (0.51-1.57), I^2=0.0% (0.0%;70.5%)
PMHK, RE (k=3)	RR 0.90 (0.43-1.87), I^2=0.0% (0.0%;70.5%)
Long-term CVD mortality	
HKSJ, RE (k=2)	RR 0.79 (0.10-6.42), I^2=0.0%
DLRE, RE (k=2)	RR 0.79 (0.55-1.14), I2=0.0%
PMHK, RE (k=2)	RR 0.79 (0.10-6.42), I^2=0.0%

DLRE: DerSimonian-Laird between-study variance estimator and Wald-type confidence intervals (standard random effect model), HKSJ: DerSimonian-Laird between-study variance estimator and Hartung-Knapp-Sidik-Jonkman adjusted confidence intervals, PMHK: Paule-Mandel between-study variance estimator and Hartung-Knapp-Sidik-Jonkman confidence intervals, RE: random effect, FE: fixed effect, k: number of studies included in the analysis.

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial

Table appendix 4.7 Estimation of effects of delayed BP lowering drug in randomised controlled trials

Methods	Delayed vs Early
Short-term all-cause mortality	
Oslo and PREVEND-IT	Peto OR 0.99 (0.43-2.27)
Long-term all-cause mortality	
Oslo and PREVEND-IT	Peto OR 0.94 (0.70-1.28)
Short-term CVD mortality	
Oslo and PREVEND-IT	Peto OR 1.26 (0.42, 3.76)
Long-term CVD mortality	
PREVEND-IT	Peto OR 2.23 (0.23-21.84)

PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial, OR: Odd Ratio.

Table appendix 4.8 Short- and long-term effects in post-hoc analysis of ALLHAT trial

Outcomes	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	O-E	V
In-Trial (1994-2002, median time 4.9 years):				
All-cause mortality	0.94 (0.66-1.35)	0.94 (0.65-1.35)	-1.78	28.77
CVD mortality	0.86 (0.45-1.67)	0.84 (0.43-1.64)	-1.50	8.57
Post-Trial (1994-2011, median time 14.1):				
All-cause mortality	0.90 (0.76-1.06)	0.89 (0.76-1.06)	-16.18	39.26
CVD mortality	0.74 (0.52-1.07)	0.77 (0.53-1.11)	-7.35	28.12

*: Adjusted for age, race, sex, diabetes mellitus, education, body mass index, smoking, aspirin, randomised group, systolic blood pressure, diastolic blood pressure, total cholesterol, serum glucose, creatinine. HR: Hazard ratio, O-E: Observed-Expected events, V: Variance. O-E and V was estimated as recommended by Tierney et al[211]. ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial, PREVEND-IT: Prevention of Renal and Vascular Endstage Disease Intervention Trial

Chapter 5

Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study (ANBP2)

Published in the journal

Journal of Clinical Lipidology 2019; 13:148-155.

Chau L.B Ho, Enayet K. Chowdhury, Monique Breslin, Jenny Doust,

Christopher M. Reid, Lindon M.H. Wing, Mark R. Nelson

Chapter 5 Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study (ANBP2).

Preface

BP and lipid lowering drug treatment (LLT) has substantively improved the major adverse cardiovascular event incidence and mortality that is attributable to the ageing population in the modern world. BP lowering drug treatment is clearly superior in the old age population who are more likely to have high CVD risk profiles than general population. Similarly, LLT is evidently superiority in the reduction of CVD incidence, however the effects on mortality in the elderly were less clear. This chapter examined the short- and long-term effect of LLT on all-cause and CVD mortality in the elderly by conducting a post-hoc analysis in the Second Australian National Blood Pressure study (ANBP2).

Abstract

Background

There is currently insufficient evidence to support the use of lipid-lowering drug treatment (LLT) for primary prevention of cardiovascular disease (CVD) in the elderly.

Objectives

We examined the relationship of early initiation of LLT with short- and long-term all-cause and CVD mortality in persons older than 65 years in this post-hoc study from the Second Australian National Blood Pressure study (ANBP2).

Methods

In- and post-trial observational study. 4257 hypertensive participants aged 65 to 84 years within Australian family practices were randomized to an angiotensin converting enzyme-inhibitor or a diuretic treatment group. After

excluding participants with a prior history of CVD, the cohort was stratified into 'LLT' and 'no LLT' subgroups based on LLT status at randomization.

Results

At randomization the participants had a mean age of 72 years, average blood pressure (BP) of 168/91 mmHg and estimated 5-year CVD risk of 18.7 ± 8.3%. In the overall study population, the association of LLT with long-term (11-years) all-cause and non-CVD mortality was significant (HR 0.78 (95% CI 0.66-0.92, p=0.003) and HR 0.70 (95% CI 0.54-0.90, p=0.006) respectively). Magnitudes of the association of LLT with long-term mortality and the association with short-term mortality were similar, however, no statistically significant association with short-term mortality was observed. In the subgroup analysis by baseline 5-year CVD risk, LLT participants in the highest risk tertile had a substantially lower relative risk for short-term all-cause mortality (HR 0.31, 95% CI 0.13-0.71, p for interaction 0.02), compared to those with lower estimated CVD risk. All analyses were adjusted for baseline and in-trial characteristics.

Conclusion

Our study showed a strong association between LLT and reduced long-term all-cause mortality. Thus, our findings support recommendations of the use of LLT in patients over 65, particularly those with high CVD risk who were more likely to obtain additional benefits in the short-term. The findings also suggested that mortality benefits of LLT for the elderly may take longer to become evident.

Introduction

The global population is ageing. In 2015 there were 617 million (8.5%) people aged over 65 years and this is likely to reach 1.6 billion (17%) by 2050 [244]. Cardiovascular disease (CVD) remains the leading burden of disease in this age group, being 30% of the total[245]. Lipid-lowering drug treatment (LLT), particularly statins, plays a key role in the prevention of CVD[130, 246, 247]. More than 40% of the Australian and US populations aged 75 and over are currently taking LLT[248, 249] and this number is projected to grow as most of the LLTs come off patent and are therefore available at lower cost.

Most of the evidence for benefits from the use of LLT in those 65 years or over are from trials of secondary prevention of CVD or in mixed populations of those with younger age [151, 152, 155, 156, 250-254], insufficient evidence is available to support the use of LLT for primary prevention in the elderly[255-258]. In a recent meta-analysis of individual patient data by the Cholesterol Treatment Trialist' Collaboration with a follow-up of 4.9 years [259], statin therapy or a more intensive statin regimen was associated with a trend of smaller relative risk reductions of major CVD events with increasing age in participants without history of CVD. In a subgroup of participants aged 65 to ≤70, statin treatment was associated with a significant reduction of major CVD with a RR 0.61 (0.51-0.73) per 1 mmol/L reduction in low density lipoprotein cholesterol, whereas no significant benefit was found in a subgroup of participants older than 70 years old. No analysis on CVD mortality or all-cause mortality in primary prevention populations was conducted in this review. A systematic review and meta-analysis by Savarese et al[154] related predominantly to primary prevention reported no significant mortality benefit of statin treatment in individuals aged 65 and over, although there were significant reductions in myocardial infarction (MI) and stroke. The average follow-up in the studies in this analysis was 3.5 years (range: 1.0 – 5.2 years): [151, 152, 155, 156, 254, 260]): this may not be long enough for the mortality benefit to reach a significant level.

A prospective cohort study with 7.3 years follow-up [261] found substantial effects of early statin use (on-treatment versus no treatment at baseline) on major CVD events and all-cause mortality in the elderly (≥ 65 years) without CVD at baseline. This result stands despite a possible dilution of effects due to 13% of non-drug users at baseline initiating treatment during the study. In contrast, another elderly cohort[262] with median follow-up at 9.1 years found no benefits for CVD or CHD events except stroke.

Evidence for both short- and long-term benefits of LLT in older adults thus remains inconsistent. From patients' perspectives, other considerations in this age group impacting on chronic drug therapy are drug adherence, the possibility of adverse drug effects and the potential for consideration of medication discontinuation when other issues such as frailty and life expectancy become dominant[263, 264]. In this current post-hoc study in a cohort

of hypertensive elderly from the Second Australian National Blood Pressure study (ANBP2)[265], we have examined the relationship between the use of LLT at randomization and short- (4 year) and long-term (11 year) all-cause and CVD mortality in those aged 65 years or over.

Methods

Study design and population

We conducted a post-hoc analysis relating to a cohort from the Second Australian National Blood Pressure study (ANBP2) [265]. ANBP2 was conducted in 1995 and was designed as a trial of a Prospective Randomized Open-label with Blinding of Endpoint assessment (PROBE). Participants aged 65-84 years at enrolment were randomized into an angiotensin-converting enzyme treatment group (enalapril recommended) or a thiazide diuretic treatment group (hydrochlorothiazide recommended) within Australian family practices. At entry, eligible participants had an average randomized blood pressure (BP) of 160/90 mmHg or over. Short-term mortality outcomes were followed for a median 4.1 years (from 1995 to 2001) as described by Wing *et al*[265]. A blinded independent endpoint committee adjudicated all study endpoints. An extended observation relating to survival status was conducted to a median 10.8 years (4.1-years in-trial and 6.7 years post-trial) using linkage to the Australian National Death Index as described by Nelson *et al*[188] to investigate longer term all-cause or CVD mortality. In this study, fatal cardiovascular events were comprised of sudden cardiac deaths, fatal stroke, fatal myocardial infarction, and 'other' cardiovascular causes of death.

To focus on primary prevention, as presented in Figure 5.1, we excluded participants who had previous CVD events at baseline (n=705) and those who were initiated on LLT (n=1292) during the clinical trial period because we were uncertain whether they were prescribed LLT due to a CVD occurrence or an increased cholesterol level. Participants were re-stratified by LLT status at entry. Subsequently, we compared the outcomes between those who were on LLT (LLT group) and those who were not (no LLT) at randomization (baseline) regardless of their randomized treatment.

ANBP2

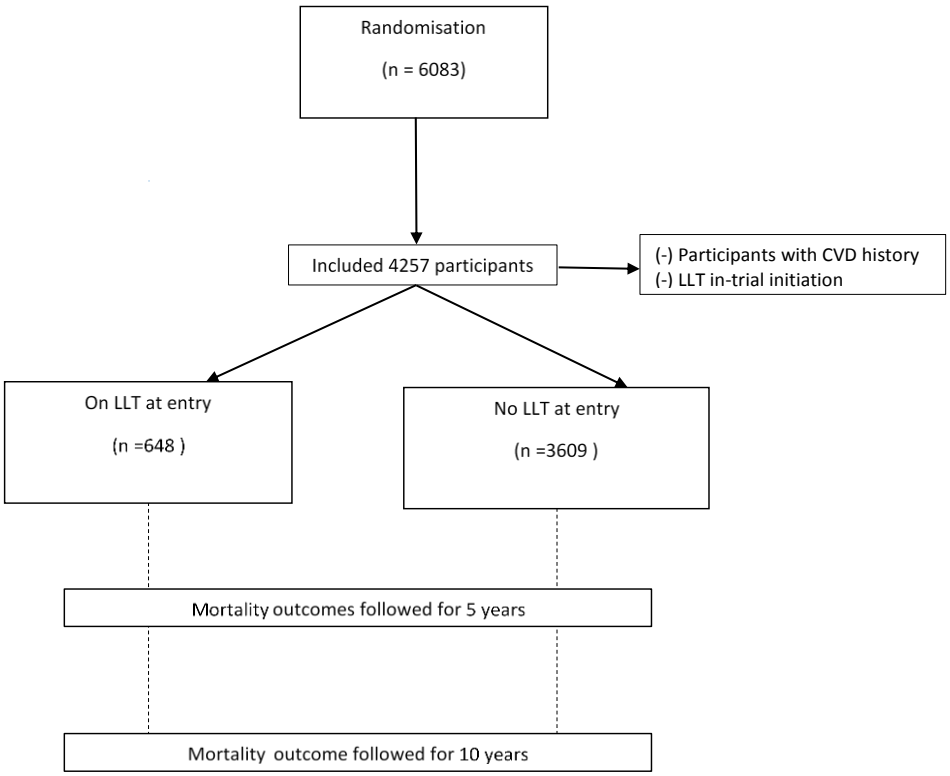


Figure 5.1 Flow chart of included participants in the analysis

LLT: Lipid lowering drug treatment, CVD: Cardiovascular disease.

Subgroup by CVD risk

To investigate how the effect of LLT was affected by baseline CVD risk, we performed a subgroup analysis stratified by tertile of 5-year predicted CVD risk score at entry. The risk score was calculated by the Framingham absolute risk equation as used in the Australian National Vascular Disease Prevention Alliance (NVDPA) guideline[2]. As per the guideline, participants were automatically scored at high risk (>15%) if they had systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg, total cholesterol > 7.5 mmol/l, diabetes and/or estimated glomerular filtration rate<45 ml/min/1.73 m^2. For participants over 75 years of age, the age value was set at 74 in the risk calculation.

Statistical analysis

The differences between the 'LLT' and 'no LLT' groups for baseline characteristics were tested by t-tests for continuous variables and Chi-square

tests for categorical variables. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and corresponding 95% confidence interval (CIs) for outcomes for participants in the 'LLT' group compared with those in 'no LLT' group. Participants were followed-up from entry to the time of event (deaths) or loss of vital status or the end of the follow-up (maximum 6 years for the short-term analysis and 11 years for the long-term analysis). Those who did not have an event throughout the observed time scale were considered as censored on 30 Sep 2001 for the short-term and 31 Oct 2009 for the long-term follow-up phase. The proportional hazard assumption was checked by a test for interaction of LLT group with time. All of the analyses were adjusted for baseline characteristics (age, sex, family history of CVD, non-HDL cholesterol, diabetes, anti-platelet use), in-trial characteristics (number of assigned in-trial BP lowering drugs), and clustered on the general practice clinic from which participants originated. Considering the multiple co-linearity issue, further adjustment models including W-H ratio and previous BP lowering treatment, systolic BP and diastolic BP at randomization were tested in sensitivity analysis. In addition, we conducted subgroup analyses stratified by age, sex and diabetes at baseline to investigate the impacts of these factors on the association of LLT and mortality outcomes. The Cox regression models were used to test for interaction of treatment in the subgroup analyses. The significance of treatment effect was set to 0.05. Data management for all analyses was performed by using Stata version 12 for Windows.

Ethics approval. ANBP2 was approved by the ethics committee of the Royal Australian College of General Practitioners and the post-trial cohort by the Monash University Standing Committee on Ethics in Research Involving Humans. The current cohort study was performed on non-identifiable dataset; thus an ethics approval was unnecessary.

Results

Patient characteristics

Our study included 4257 out of the original ANBP2 cohort of 6083 participants, approximately 70% of the total ANBP2 cohort. As shown in Table 5.1, at study entry, participants had a mean age of 72 years, mean BP of 168/91

mmHg, mean plasma total cholesterol of 5.5 ± 0.9 mmol/l and HDL cholesterol of 1.4 ± 0.5 mmol/l. Compared with the 'no LLT' group, more female and younger participants were on LLT at baseline. Also, LLT participants were more likely to have a family history of CVD, diagnosed diabetes mellitus, and be on antiplatelet and previous BP lowering drug treatment. Although these participants were on LLT, they still had higher average plasma total cholesterol level and non-HDL cholesterol. This may be attributable either to insufficient adherence to LLT or to the non-specific treatment target recommended at the time (1995-2001) for primary prevention. In general, based on the estimated risk over 5-year, all participants were at high risk of CVD – mean risk: 18.7% ± 8.3% using the Anderson equation[43] as per the Australian NVDPA guideline[2]. The estimated CVD risk score of the no LLT group (18.9% ± 8.3%) was slightly higher than the LLT group, suggesting that LLT was prescribed based on the participant's cholesterol level, not on absolute CVD risk.

Table 5.1 Baseline characteristics by lipid-lowering drug treatment.

	Total (N=4257)	**No LLT (n=3609)**	**LLT (n=648)**	**p-value**
Age (mean ± SD in years)	72.0 ± 5.0	**72.1 ± 5.0**	**71.0 ± 4.4**	**<0.001**
Female sex n (%)	2195 (51.6)	**1789 (49.6)**	**406 (62.7)**	**<0.001**
Current smoker n (%)	305 (7.2)	260 (7.2)	45 (6.9)	0.81
Systolic BP at randomization (mean ± SD, mmHg)	167.6 ± 12.6	167.7 ± 12.6	167.4 ± 12.3	0.58
Diastolic BP at randomization (mean ± SD, mmHg)	90.8 ± 8.1	90.8 ± 8.1	90.8 ± 7.9	0.89
TC (mean ± SD, mmol/l)	5.5 ± 0.9	**5.5 ± 0.9**	**5.8 ± 1.1**	**<0.001**
HDL-c (mean ± SD, mmol/l)	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	0.48
Non-HDL cholesterol (mean ± SD, mmol/l)	4.2 ± 1.0	**4.1 ± 0.9**	**4.4 ± 1.1**	**<0.001**
BMI (mean ± SD, kg/m2)	27.0 ± 4.2	27.0 ± 4.2	27.2 ± 4.1	0.18

	Total (N=4257)	No LLT (n=3609)	LLT (n=648)	p-value
5-year Framingham risk score (mean ± SD, %)	18.7 ± 8.3	**18.9 ±8.3**	**17.8 ± 8.1**	**<0.001**
Diabetes mellitus n (%)	275 (6.5)	**217 (6.0)**	**58 (9.0)**	**0.01**
Waist circumference (mean ± SD, cm)	94.4 ± 12.1	94.6 ± 12.2	93.6 ± 11.8	0.07
W-H ratio	0.90 ± 0.08	**0.90 ± 0.08**	**0.89 ± 0.08**	**0.004**
Current alcohol consumption n (%)	3126 (73.4)	2660 (73.7)	466 (71.9)	0.34
Physically active n (%)	3332 (78.3)	2815 (78.0)	517 (79.8)	0.31
Education n (%)				0.57
Primary school	997 (23.4)	854 (23.7)	143 (22.1)	
High school not completed	1853 (43.5)	1560 (43.2)	293 (45.2)	
Competed high school or higher	1407 (33.1)	1195 (33.1)	212 (32.7)	
Socio-economic status n (%)				0.66
1st quartile (most advantaged)	1085 (25.5)	915 (25.4)	170 (26.2)	
2nd quartile	1151 (27.0)	969 (26.9)	182 (28.1)	
3rd quartile	1365 (32.1)	1171 (32.5)	194 (29.9)	
4th quartile (most disadvantage)	656 (15.4)	554 (15.4)	102 (15.7)	
Family history of CVD n (%)				**<0.001**
Yes	1986 (46.7)	**1604 (44.4)**	**382 (59.0)**	
Unknown	496 (11.7)	**423 (11.7)**	**73 (11.3)**	
Random blood glucose (mean ± SD, mmol/l)	5.5 ± 1.8	5.5 ± 1.8	5.6 ± 1.9	0.33
Serum creatinine (mean ± SD, µmol/l)	90.8 ± 19.2	90.8 ± 19.2	90.8 ± 18.9	0.96

	Total (N=4257)	No LLT (n=3609)	LLT (n=648)	p-value
Antiplatelet use n (%)	433 (10.2)	**341 (9.5)**	**92 (14.2)**	**<0.001**
Previous BP lowering treatment, n (%)	2556 (60.0)	**2077 (57.6)**	**479 (73.9)**	**<0.001**

LLT: lipid-lowering drug treatment, BP: blood pressure, HDL-c: high-density lipoprotein cholesterol, TC: total cholesterol, BMI: body mass index, W-H ratio: waist-hip ratio, CVD: cardiovascular disease. **Bold** p<0.05

For in-trial characteristics (Table 5.2), there was no significant difference between the number of 'LLT' and 'no LLT' participants randomized to either ACE-I or diuretic-based therapy. However, LLT participants were more likely to receive a higher number of randomized drugs and had a lower average on-treatment diastolic BP.

Table 5.2 In-trial characteristics by LLT stratification.

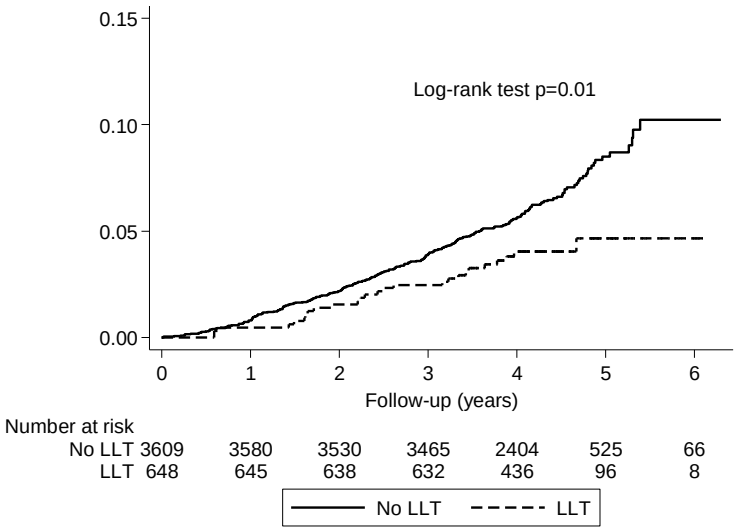
	Total (N=4257)	No LLT (n=3609)	LLT (n=648)	p-value
Randomized to ACE-I n (%)	2117 (49.7)	1782 (49.4)	355 (51.7)	0.28
BP lowering-drug compliance n (%)	1828 (67.2)	1532 (67.3)	296 (66.2)	0.64
Average on-treatment systolic BP (mean ± SD, mmHg)	145.6 ± 9.9	145.6 ± 9.9	145.4 ± 9.6	0.49
Average on-treatment diastolic BP (mean ± SD, mmHg)	80.8 ± 5.5	**80.8 ± 5.5**	**80.3 ± 5.2**	**0.02**
Number of assigned in-trial BP lowering drugs n (%)				**<0.001**
0	195 (4.6)	**175 (4.9)**	**20 (3.1)**	
1	2183 (51.6)	**1902 (53.0)**	**281 (43.4)**	
2	1640 (38.7)	**1336 (37.3)**	**304 (46.7)**	
≥3	216 (5.1)	**174 (4.9)**	**42 (6.5)**	

LLT: lipid-lowering drug treatment, ACE-I: Angiotensin Converting Enzyme-Inhibitor, BP: blood pressure. Bold p<0.05

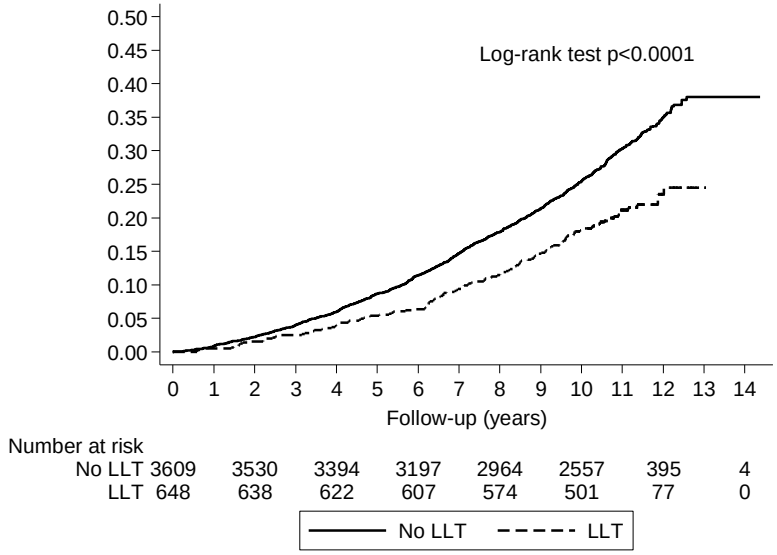
Association of LLT and mortality in the total cohort

263 deaths (106 CVD deaths including 13 fatal myocardial infarction, 28 fatal stroke and 65 other CVD deaths) occurred during the in-trial period (median 4.1 years/'short-term'). These numbers increased to an overall 1250 deaths (622 CVD deaths including 124 fatal myocardial infarction, 122 fatal stroke and 376 other CVD deaths) by the end of the extended phase (median 10.8 years/'long-term'). Accumulative incidences of events according to LLT were presented in KM curves in Figure 5.2 and Figure appendix 5.1).

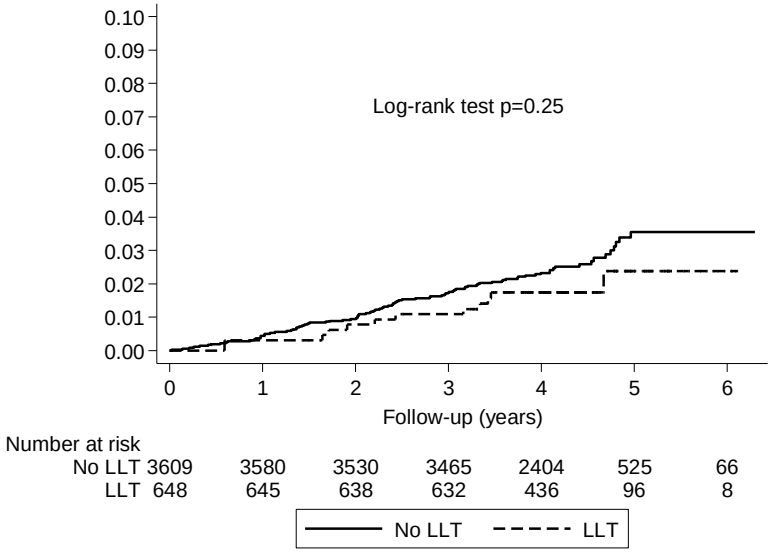
In the long-term (10.8 years), LLT participants had a significantly lower adjusted risk of all-cause mortality HR 0.78 (95% CI 0.66-0.92, p=0.003). Noticeably, most of the survival benefits were attributable to the effects on long-term non-CVD deaths HR 0.70 (95% CI 0.54-0.90, p=0.006), particularly cancer deaths HR 0.62 (95% CI 0.44-0.88, p=0.007) (Table 5.3). Also, magnitudes of the association of LLT with long-term mortality and the association with short-term mortality were similar, however, no statistically significant association on short-term mortality was observed (Table 5.3 and Table 5.4). In terms of CVD mortality, there was no significant difference between the LLT and no LLT groups in either the short (HR 0.86, 95% CI 0.46-1.61) or long term (HR 0.87, 95% CI 0.68-1.11).



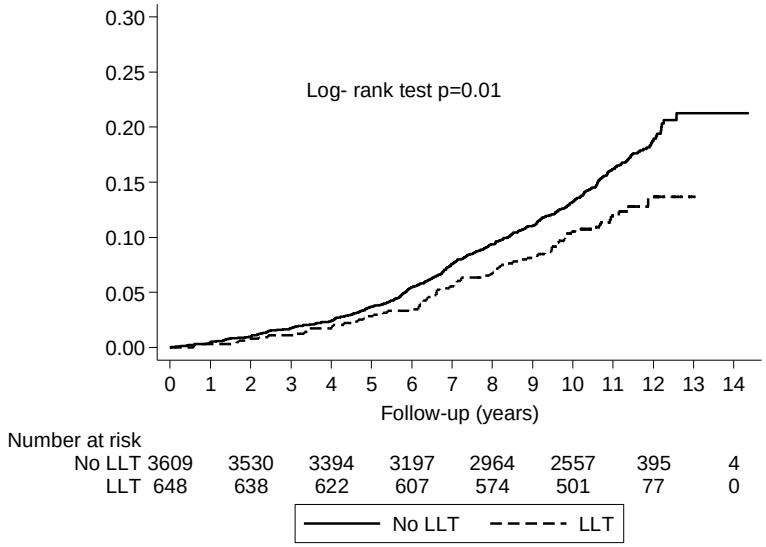
(A) Short-term all-cause mortality



(B) Long-term all-cause mortality



(C) Short-term CVD mortality



(A) Long-term CVD mortality

Figure 5.2 Cumulative incidence of all-cause and CVD mortality according to LLT (Kaplan Meier curve) in short- and long-term follow-up.

LLT: lipid-lowering treatment, CVD: cardiovascular disease.

Table 5.3 Association between LLT and long-term mortality in tertiles by estimated 5-year CVD risk and in the total cohort.

		Event			
	Number of events % (n)	(rate per 1000 person-year)		Univariate	Adjusted *
Tertiles by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
All-cause mortality					
1st tertile (2-14.5%)	7.0 (297)	11.5	22.5	**0.51 (0.35-0.74)**	**0.64 (0.44-0.94)**
2nd tertile (14.5-22.6%)	9.3 (398)	21.7	29.6	**0.72 (0.53-0.98)**	0.85 (0.62-1.16)
3rd tertile (22.6-59.8%)	13.1 (557)	30.7	43.3	**0.70 (0.53-0.91)**	0.85 (0.65-1.11)
Total	29.4 (1252)	20.6	31.6	**0.64 (0.54 - 0.76)**	**0.78 (0.66-0.92)**
p for interaction	-	-	-	0.29	0.29
CVD mortality					
1st tertile (2-14.5%)	3.3 (141)	5.9	10.5	**0.56 (0.33-0.95)**	0.74 (0.43-1.26)
2nd tertile (14.5-22.6%)	4.6 (196)	10.9	14.5	0.74 (0.48-1.14)	0.86 (0.53-1.38)
3rd tertile (22.6-59.8%)	6.6 (282)	17.9	21.4	0.82 (0.58-1.16)	0.98 (0.69-1.38)

	Number of events % (n)	Event (rate per 1000 person-year)		Univariate	Adjusted *
Tertiles by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
Total	14.5 (619)	11.1	15.4	**0.71 (0.56 - 0.91)**	0.87 (0.68-1.11)
p for interaction	-	-	-	0.5	0.46
Cancer death					
1st tertile (2-14.5%)	2.0 (87)	2.4	6.8	**0.35 (0.15-0.80)**	**0.40 (0.17-0.93)**
2nd tertile (14.5-22.6%)	2.9 (125)	7.1	9.3	0.76 (0.44-1.29)	0. 86(0.50-1.47)
3rd tertile (22.6-59.8%)	3.7 (157)	6.9	12.5	**0.55 (0.32-0.95)**	0.62 (0.35-1.08)
Total	8.7 (369)	5.3	9.5	**0.55 (0.39 - 0.78)**	**0.62 (0.44-0.88)**
p for interaction	-	-	-	0.27	0.28
Non-CVD death					
1st tertile (2-14.5%)	3.7 (156)	5.5	11.9	**0.46 (0.27-0.80)**	**0.57 (0.33-0.98)**
2nd tertile (14.5-22.6%)	4.7 (202)	10.9	15.1	0.71 (0.46-1.09)	0.84 (0.55-1.30)

		Event			
	Number of events % (n)	(rate per 1000 person-year)		Univariate	Adjusted *
Tertiles by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
3rd tertile (22.6-59.8%)	6.5 (275)	12.9	21.8	**0.58 (0.39-0.87)**	0.72 (0.48-1.08)
Total	14.9 (633)	9.5	16.2	**0.57 (0.44-0.74)**	**0.70 (0.54-0.90)**
p for interaction	-	-	-	0.47	0.48

LLT: lipid-lowering treatment, CVD: cardiovascular disease. * Age, sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. Bold p<0.05.

Table 5.4 Association between LLT and short-term mortality in tertiles by estimated 5-year CVD risk and in the total cohort.

	Number of events % (n)	Event (rate per 1000 person-year)		Univariate	Adjusted *
Tertile by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
All-cause mortality					
1st tertile (2-14.5%)	1.2 (52)	7.0	9.3	0.76 (0.34-1.67)	0.92 (0.41-2.07)
2nd tertile (14.5-22.6%)	1.8 (76)	14.7	12.5	1.17 (0.64-2.12)	1.39 (0.74-2.60)
3rd tertile (22.6-59.8%)	3.1 (134)	6.9	24.9	**0.28 (0.12-0.64)**	**0.32 (0.14-0.75)**
Total	6.2 (262)	9.4	15.7	**0.60 (0.40-0.90)**	0.71 (0.47-1.07)
p for interaction	-	-	-	**0.01**	**0.02**
CVD mortality					
1st tertile (2-14.5%)	0.4 (15)	2.0	2.8	0.70 (0.16-3.08)	1.12 (0.23-5.39)
2nd tertile (14.5-22.6%)	0.8 (32)	7.9	5.1	1.54 (0.67-3.56)	1.78 (0.71-4.47)
3rd tertile (22.6-59.8%)	1.3 (57)	3.5	10.4	0.33 (0.10-1.07)	0.35 (0.11-1.14)
Total	2.4 (104)	4.3	6.2	0.71 (0.39 - 1.29)	0.86 (0.46-1.61)

	Number of events % (n)	Event (rate per 1000 person-year)		Univariate	Adjusted *
Tertile by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
p for interaction	-	-	-	0.09	0.1
Cancer death					
1st tertile (2-14.5%)	0.5 (23)	3.0	4.0	0.74 (0.22-2.49)	0.77 (0.23-2.55)
2nd tertile (14.5-22.6%)	0.8 (35)	5.6	5.9	0.96 (0.37-2.48)	1.14 (0.44-3.00)
3rd tertile (22.6-59.8%)	1.1 (48)	2.3	8.9	0.26 (0.06-1.08)	0.27 (0.06-1.18)
Total	2.5 (106)	3.6	6.3	0.58 (0.30-1.11)	0.60 (0.31-1.17)
p for interaction	-	-	-	0.26	0.28
Non-CVD death					
1st tertile (2-14.5%)	0.9 (37)	5.0	6.4	0.78 (0.30-2.00)	0.85 (0.33-2.18)
2nd tertile (14.5-22.6%)	44 (1.0)	6.8	7.4	0.91 (0.39-2.16)	1.12 (0.46-2.73)
3rd tertile (22.6-59.8%)	1.8 (77)	3.5	14.5	**0.24 (0.08-0.77)**	**0.29 (0.09-0.96)**
Total	3.7 (158)	5.1	9.5	**0.53 (0.31-0.93)**	0.61 (0.35-1.06)

	Number of events % (n)	Event (rate per 1000 person-year)		Univariate	Adjusted *
Tertile by estimated 5-year CVD risk		**LLT**	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
p for interaction	-	-	-	0.13	0.17

LLT: lipid-lowering treatment, CVD: cardiovascular disease. * Age, sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. Bold p<0.05.

Association of LLT and mortality in a subgroup by 5-year estimated CVD risk

In the subgroup analysis by estimated absolute CVD risk at baseline (Table 5.3 & Table 5.4), heterogeneity was found for short-term all-cause mortality, but no other outcomes. In the highest risk tertile, LLT group had a reduced risk of short-term all-cause mortality (HR 0.32, 95% CI 0.14-0.75) with p for interaction of 0.02, compared to the low and moderate risk tertile. There was no effect seen in other outcomes in the short or long-term.

Sensitivity analysis

In subgroup analyses stratified by age, sex and diabetes status at baseline (Table appendix 5.1 and Table appendix 5.2), regarding long-term and short-term associations between LLT and mortality outcomes, the associations were not statistically different among stratified subgroups. In a further adjusted model, we added characteristics that were statistically different between the LLT group (W-H ratio and previous BP lowering treatment, systolic BP and diastolic BP at randomization) in the adjusted model. The results were similar to the adjusted model, and no substantial difference was recorded.

Discussion

In this post-hoc analysis of ANBP2, we found a positive association between LLT with long-term all-cause, non-CVD and cancer mortality, but the protective association with CVD mortality did not reach statistical significance. For short-term outcomes, no significant association was recorded, although the magnitudes of the associations (HRs) were similar to the long-term effects.

Our long-term findings are consistent with the long-term ASCOT-LLA trial[266] and a 7.3-year observational study[261]. All three studies found a significant reduction in all-cause mortality and a non-significant reduction in CVD mortality. Surprisingly, similar to our study, ASCOT-LLA also observed a significant benefit on long-term non-CVD deaths (HR 0.85, 95%CI 0.73-0.99). Our study recorded a substantial benefit of LLT on cancer deaths, whereas ASCOT-LLA reported a non-significant effect on cancer deaths (HR 0.92, 95%CI 0.76-1.12), but a significant effect on deaths related to infectious or respiratory diseases (HR 0.64, 95% CI 0.42-0.97). The ANBP2 study did not

record these outcomes, so we were unable to include these in this analysis. A limitation of our findings is that cancer deaths in both the short- and long-term may be confounded by the status of diagnosed cancer at entry. If the prevalence of diagnosed cancer at study entry were equally distributed between LLT and no LLT group, our results would support findings from previous studies showing a substantial reduction of cancer-related deaths by statin treatment in participants either with pre-existing cancer or no cancer[267, 268]. In contrast, two meta-analyses[247, 269] of large randomised controlled trials showed no beneficial effect of statins on cancer-related deaths. Yet, most of these RCTs had a high proportion of participants with previous CVD.

In terms of the short-term outcomes, our findings on all-cause and CVD mortality are consistent with a previous meta-analysis by Savarese[154] who reported a non-significant effect of LLT on all-cause mortality with an RR 0.94 (95% CI 0.86-1.04; p=0.21) and on CVD mortality with an RR 0.91 (95% CI 0.69-1.20; p=0.49) with a mean follow-up of 3.5 years (range: 1 to 5.2 years). However, in our study, the protective association for all-cause mortality reached statistical significance in the long-term analysis with the median follow-up time of 10.8 years, suggesting that differences in mortality may take longer to accrue.

In the subgroup analysis by CVD risk, LLT showed a greater effect on short-term all-cause mortality in the highest risk tertile, compared to other lower risk groups. We did not find any significant difference in the low or moderate risk groups regarding other trial endpoints. In contrast to our results, the Cholesterol Treatment Trialists (CTT)' Collaborators[247] observed a substantial reduction of all-cause mortality on the total cohort 0.91 (95%CI 0.85-0.97) but a non-statistically significant heterogeneity (p for trend=0.2) among risk subgroups (5-year risk at baseline <5%, ≥5% and <10%, ≥10% and <20%, ≥20% and <30%, ≥30%). The CTT meta-analysis included participants at both middle and old age.

Limitations

Due to the nature of the post-hoc observational design, our findings are open to residual confounding, and thus should be interpreted with caution. The

results are also only based on one study, so are limited by low power. Another limitation of our study is missing details of LLT at baseline and in the post-trial period including reason for prescription, dose, duration and adherence to treatment. Compared to the 'no LLT' group, LLT participants had a substantially higher total cholesterol and were more likely to have previous BP lowering and antiplatelet use, to be diabetic and to have a family history of CVD suggesting that they were at higher underlying baseline risk. Covariate adjustment has limited ability to control for 'confounding by indication'. In the subgroup analysis by estimated CVD risk, age, sex and diabetes at baseline (

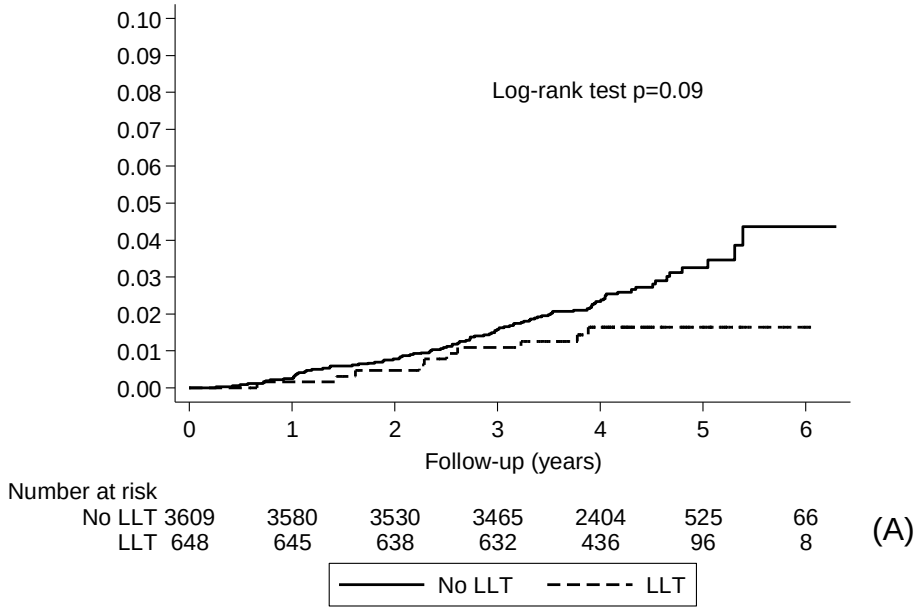
Table appendix 5.1), the magnitudes of the association between LLT and mortality were similar in stratified groups, except that the association between LLT and short-term all-cause mortality varied according to estimated CVD risk. The association between LLT and other short-term or long-term mortality was found to be independent of age, sex, diabetes and estimated CVD risk. Furthermore, confounding by indication would be expected to bias in favor of higher mortality in the LLT group. A final point is that the risk algorithm is for untreated populations in both groups, but underestimation should affect those in the LLT group to a greater extent as they were on lipid-lowering therapy.

In conclusion, our study supports the early use of LLT in those 65 years or over due to the association with long-term benefits on all-cause mortality, although the short-term benefits are likely to be evident only in the high-risk population. The findings suggest that the mortality benefit of LLT for the elderly may take longer to become evident.

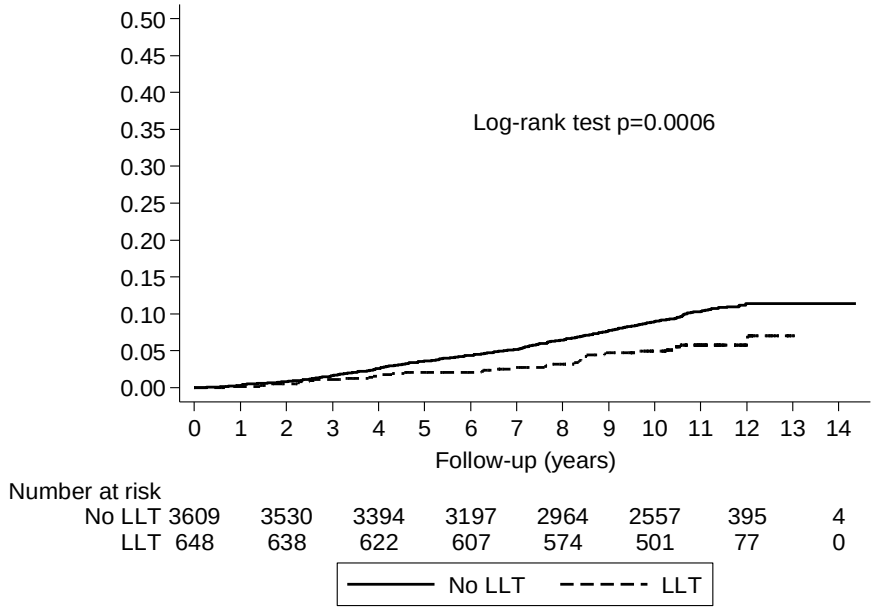
Postscripts

This chapter showed a 'delayed benefits' of lipid lowering drug treatment in the elderly of 65 years or over that may take at least ten years to become evident, although the treated high-risk people obtained early benefits on reduced risk of all-cause mortality. The next chapter would summarize the key findings, their implications and present future directions of research.

Appendix



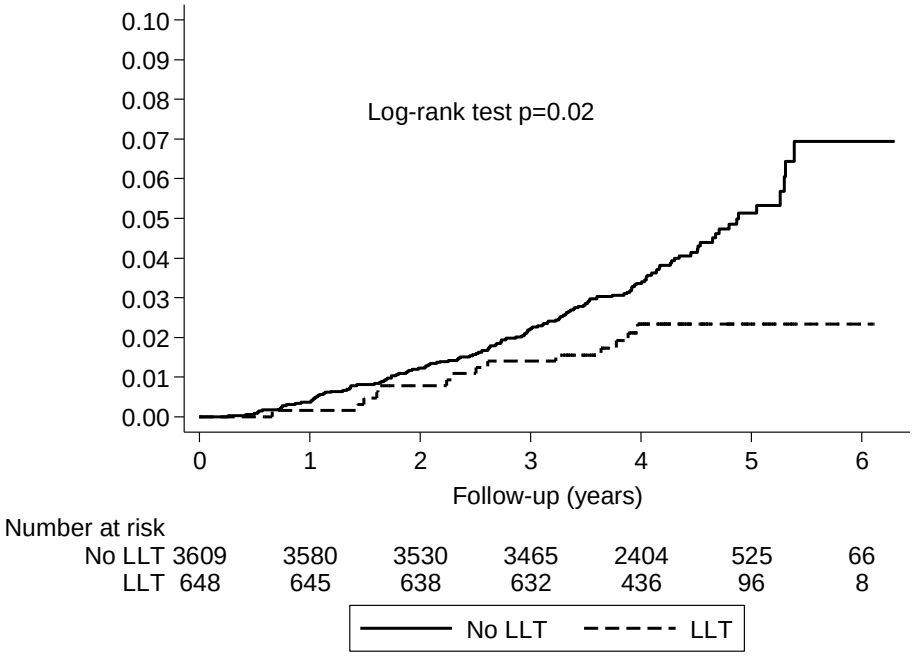
(A)



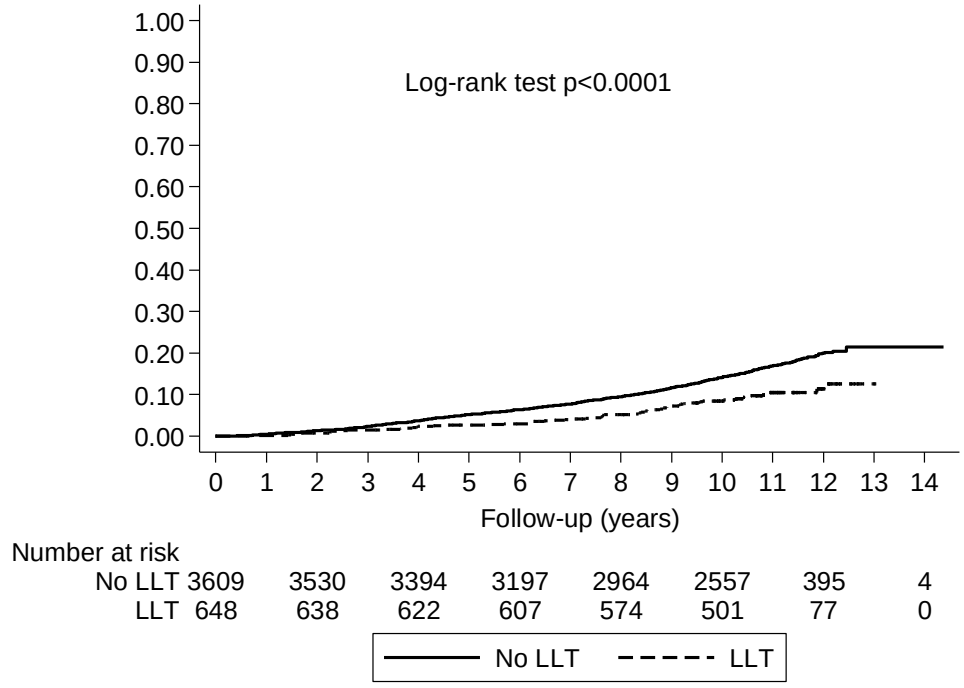
(B)

Figure appendix 5.1 Cumulative incidence of cancer mortality according to LLT in short- and long-term follow-up (Kaplan Meier curve).

LLT: lipid-lowering treatment, CVD: cardiovascular disease. (A): Short-term period. (B): Long-term period.



(A)



(B)

Figure appendix 5.2 Cumulative incidence of non-CVD mortality according to LLT in short- and long-term follow-up (Kaplan Meier curve).

LLT: lipid-lowering treatment, CVD: cardiovascular disease. (A): Short-term period. (B): Long-term period.

Table appendix 5.1. Association between LLT and long-term mortality stratified by age, sex and diabetes status at baseline.

	Event (rate per 1000 person-year)		**Univariate**	**Adjusted ***
	LLT	**No LLT**	**HR (95%CI)**	**HR (95%CI)**
All-cause mortality				
Age				
<75	15.5	22.7	**0.68 (0.53-0.85)**	**0.74 (0.59-0.94)**
≥ 75	38.4	52.3	**0.72 (0.55-0.94)**	**0.73 (0.56-0.97)**
p for interaction	-	-	0.73	0.88
Sex				
Males	22.9	35.7	**0.63 (0.48-0.83)**	**0.73 (0.56-0.94)**
Females	19.2	27.6	**0.69 (0.54-0.87)**	0.82 (0.66-1.04)
p for interaction	-	-	0.62	0.52
Diabetes				
No	19.3	30.8	**0.62 (0.51-0.75)**	**0.77 (0.64-0.93)**
Yes	32.9	44.5	0.70 (0.43-1.14)	0.79 (0.51-1.22)
p for interaction	-	-	0.62	0.87
CVD mortality				
Age				
<75	7.3	9.9	0.74 (0.52-1.04)	0.80 (0.57-1.12)
≥ 75	24.2	28.2	0.84 (0.60-1.19)	0.84 (0.59-1.19)
p for interaction	-	-	0.59	0.69
Sex				
Males	12.3	17.1	0.71 (0.48-1.03)	0.80 (0.55-1.17)
Females	10.4	13.7	0.76 (0.55-1.04)	0.94 (0.67 -1.30)
p for interaction	-	-	0.77	0.63
Diabetes				

	Event (rate per 1000 person-year)		Univariate	Adjusted *
	LLT	No LLT	HR (95%CI)	HR (95%CI)
No	10.4	14.9	**0.69 (0.53-0.90)**	0.88 (0.68-1.16)
Yes	18.1	24.2	0.71 (0.37-1.37)	0.80 (0.43-1.48)
p for interaction	-	-	0.93	0.8
Cancer mortality				
Age				
<75	5.2	8.2	**0.63 (0.42-0.94)**	0.69 (0.45-1.04)
≥ 75	5.4	12.5	**0.43 (0.21-0.88)**	**0.45 (0.22-0.92)**
p for interaction	-	-	0.34	0.32
Sex				
Males	5.3	11.3	**0.46 (0.26-0.81)**	**0.50 (0.29-0.84)**
Females	5.2	7.7	0.68 (0.43-1.06)	0.73 (0.47-1.14)
p for interaction	-	-	0.29	0.26
Diabetes				
No	5.1	9.5	**0.53 (0.37-0.77)**	**0.61 (0.42-0.87)**
Yes	6.6	9.4	0.67 (0.23-1.98)	0.79 (0.29-2.17)
p for interaction	-	-	0.68	0.73
Non-CVD mortality				
Age				
<75	8.1	12.8	**0.63 (0.45-0.87)**	**0.70 (0.50-0.98)**
≥ 75	14.1	24.1	**0.58 (0.37-0.90)**	**0.60 (0.39-0.94)**
p for interaction	-	-	0.76	0.66
Sex				
Males	10.6	18.5	**0.56 (0.38-0.84)**	**0.66 (0.45-0.97)**
Females	8.8	14.0	**0.62 (0.44-0.88)**	0.72 (0.51-1.02)
p for interaction	-	-	0.7	0.67
Diabetes				

	Event (rate per 1000 person-year)		Univariate	Adjusted *
	LLT	No LLT	HR (95%CI)	HR (95%CI)
No	8.9	16.0	**0.55 (0.42-0.73)**	**0.68 (0.52-0.89)**
Yes	14.8	20.3	0.69 (0.34-1.42)	0.69 (0.34-1.42)
p for interaction	-	-	0.56	0.65

LLT: lipid-lowering treatment, CVD: cardiovascular disease. * Sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. Bold p<0.05.

Table appendix 5.2 Association between LLT and short-term mortality stratified by age, sex and diabetes status at baseline.

	Event (rate per 1000 person-year)		Univariate	Adjusted *
	LLT	No LLT	HR (95%CI)	HR (95%CI)
All-cause mortality				
Age				
<75	7.1	11.7	0.61 (0.35-1.04)	0.67 (0.39-1.17)
≥ 75	17.1	24.1	0.71 (0.38-1.32)	0.71 (0.37-1.34)
p for interaction	-	-	0.70	0.85
Sex				
Males	12.6	18.1	0.70 (0.39-1.23)	0.78 (0.43-1.42)
Females	7.5	13.2	0.57 (0.32-1.02)	0.64 (0.35-1.17)
p for interaction	-	-	0.64	0.63
Diabetes				
No	9.6	15.1	**0.64 (0.42-0.97)**	0.79 (0.51-1.21)
Yes	7.8	25.4	0.31 (0.07-1.30)	0.24 (0.04-1.39)
p for interaction	-	-	0.29	0.28
CVD mortality				
Age				
<75	3.3	4.1	0.80 (0.36-1.77)	0.90 (0.39-2.07)
≥ 75	7.8	10.4	0.75 (0.30-1.87)	0.71 (0.27-1.82)
p for interaction	-	-	0.92	0.76
Sex				

	Event (rate per 1000 person-year)		Univariate	Adjusted *
	LLT	No LLT	HR (95%CI)	HR (95%CI)
Males	7.8	7.6	1.02 (0.49-2.14)	1.12 (0.50-2.50)
Females	2.3	4.7	0.49 (0.17-1.37)	0.59 (0.20-1.77)
p for interaction	-	-	0.24	0.26
Diabetes				
No	4.4	5.6	0.78 (0.42-1.46)	1.09 (0.55-2.15)
Yes	3.9	14.3	0.28 (0.04-2.11)	0.14 (0.01-1.56)
p for interaction	-	-	0.27	0.22
Cancer mortality ¶				
Age				
<75	3.3	5.2	0.63 (0.29-1.39)	0.69 (0.31-1.54)
≥ 75	4.7	8.6	0.55 (0.17-1.77)	0.48 (0.14-1.62)
p for interaction	-	-	0.83	0.77
Sex				
Males	2.9	6.8	0.43 (0.13-1.37)	0.43 (0.12-1.43)
Females	4.1	5.8	0.70 (0.31-1.55)	0.73 (0.32-1.66)
p for interaction	-	-	0.49	0.48
Non-CVD mortality				
Age				
<75	3.8	7.5	0.50 (0.24-1.04)	0.55 (0.26-1.15)
≥ 75	9.3	13.7	0.69 (0.30-1.59)	0.70 (0.29-1.66)
p for interaction	-	-	0.58	0.64
Sex				
Males	4.9	10.5	0.46 (0.17-1.13)	0.52 (0.21-1.30)
Females	5.2	8.4	0.62 (0.31-1.24)	0.67 (0.33-1.36)
p for interaction	-	-	0.60	0.63
Diabetes				
No	5.2	9.4	**0.55 (0.31-0.98)**	0.63 (0.36-1.13)
Yes	3.9	11.0	0.34 (0.04-2.69)	0.28 (0.02-3.33)
p for interaction	-	-	0.65	0.69

LLT: lipid-lowering treatment, CVD: cardiovascular disease. * Sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. ¶ Subgroup by diabetes status was not reported due to lack of event in diabetes group. Bold p<0.05

Chapter 6

Summary, implications, future directions and conclusions

Chapter 6 Summary, implications, future directions and conclusions

Summary of background

Cardiovascular disease (CVD) remains the major burden of disease worldwide and is no longer limited to developed countries: the so-called "epidemiologic transition" [10]. It is anticipated that deaths due to CVD would continuously increase in the next few years in both developed and developing countries due to ageing[30-33]. Blood pressure and lipid lowering drug treatment have been the two most effective drug therapies in the primary prevention of CVD. Their benefits are mostly observed in the secondary prevention population or in individuals at high CVD risk, Thus, preventive drug therapies are now recommended based on absolute CVD risk, not on traditional individual BP or blood lipid thresholds. There is a persistent belief [85, 109-111] of 'irreversible damage' if not treating high BP at a traditional threshold of 140 mmHg, although strong evidence[70, 74, 84, 88-93] for the beneficial effects of BP lowering drug treatment were limited to high risk individuals as mentioned above. Similarly, there is a lack of evidence for the benefit of lipid lowering drug treatment on mortality in the elderly because the evidence was established when most of the elderly are eligible for a drug therapy according to the current absolute risk guidelines (age is the main driver of the risk estimation). The current research investigated short- and long-term adverse effects of not treating high blood pressure in 'healthy' adults and short and long-term effects of lipid lowering drug treatment in the 'healthy' elderly

Summary of results

Blood pressure lowering drug treatment was associated with a clinically significant absolute risk reduction of major CVD events and all-cause mortality in the highest CVD risk tertile. The magnitudes of absolute risk reductions linearly increased from low to high tertile at any study endpoints, although the heterogeneity was only statistically significant for all-cause mortality. In contrast, stratification by tertile of baseline BP did not result in such a trend and no heterogeneity of treatment effect was found. These findings ~~reaffirm~~ contribute further evidence to the rationale of treating high BP based on

absolute CVD risk estimation incorporating major risk factors rather than BP level alone.

In hypertensive individuals with at least one more CVD risk factor, previously untreated high BP tended to be associated with a lower risk of all-cause and CVD mortality at 10-year and 14-year follow-up compared to previously treated BP. Of note, the blood pressure of previously untreated participants was more easily controlled with fewer medications needed to reach a treatment target (BP <140/90 mmHg) compared to the previously treated group. When these factors were adjusted for, the association between previously untreated group and lower risk of mortality became non-significant. No substantial 'harm' in 'previously untreated' individuals was found in the high CVD risk subgroup (10-year Framingham risk score>30%).

In middle-aged adults with mildly elevated BP, no evidence of adverse 'legacy effect' on all-cause and CVD mortality or major CVD event of not treating high BP at a threshold of 140 mmHg was recorded in either short-term follow-up (median follow-up 4-6 years) or long-term period of more than 10 years (median follow-up 10-40 years). The non-significant effects on long-term all-cause and CVD mortality of 'untreated' status were consistent across the absolute CVD risk subgroups (low:<20% 10-year Framingham risk score, moderate:20-30%, high: >30%).

In the hypertensive elderly, lipid lowering drug treatment was associated with a 'delayed benefit' on all-cause mortality that took longer than five years to become evident, however high CVD risk individuals may have had an earlier beneficial effect than those with low or moderate CVD risk profiles.

Strengths and limitations of this research

The research incorporated data from large multi centres randomised controlled trials (ANBP, ALLHAT and ANBP2) in which blood pressure lowering drug treatments, major risk factors and hard CVD outcomes were systematically measured and assessed in a median follow-up of at least four years.

However, there are some major limitations as outlined following:

1). Post-hoc analysis carries risk of selection bias.

The post-hoc analyses conducted in ALLHAT (chapter 4) and ANBP2 (chapter 5) was limited to participants with no history of CVD. Excluded participants with previous CVD events had substantially higher CVD risk than the general population. Also, we do not know whether these baseline CVD events occurred before or after the use of previous drug treatment. After excluding these participants, some characteristics between those with and without previous drug treatment remained imbalanced. The bias was in favour of higher mortality in the treatment group. However, the magnitude of the effect on long-term all-cause mortality after adjustment for these imbalance characteristics decreased and became non-significant regarding BP lowering drug treatment and remained significant regarding lipid lowering drug treatment.

2). Observational studies of ALLHAT (chapter 4) and ANBP2 (chapter 5) are subject to confounding by indication.

The main exposure in the ALLHAT and ANBP2 are the previous use of BP or lipid lowering drug treatment correspondingly. Compared with the untreated population, participants with the early use of such preventive drug treatment were more likely to have higher underlying CVD risk at baseline. These participants could have been exposed to longer periods of high BP or lipid, or failed to implement lifestyle modifications. Thus, confounding by indication would bias in favour of higher mortality in treatment group.

3). The lack of information on previous BP and lipid lowering drug treatment such as duration of treatment, pre-treatment BP and blood lipid level, adherence to treatment, etc limits interpretation of the data.

4). The systematic review and meta-analysis included a small number of studies.

5). Only mortality outcomes were reported in short- and long-term follow-up, while non-fatal events were not assessed in long-term follow-up.

Future directions

Assuming the above limitations of the research, a gold standard randomised controlled trial would ideally examine effects of not initiating BP lowering drug treatment in 'healthy' adults. However, due to the long-term established association between high BP and CVD risk, a 'no drug treatment or placebo' arm is not likely to be ethically possible even when lifestyle modifications are done because lifestyle changes alone are not considered sufficient to control BP and individuals do not adhere to lifestyle advices as well as drug treatment[173]. Also, a study on low or moderate risk people or those with mildly elevated BP requires an enormous sample size or long-term follow-up to reach the sufficient power to identify a significant difference between 'treatment' and 'no treatment'. In spite of the above challenges, a post-hoc study of a randomised controlled trial that records details of pre-trial BP lowering drug treatment, non-fatal outcomes (e.g. stroke or coronary heart disease) or safety outcomes (hypotension, syncope, electrolyte abnormalities, acute kidney injury, or acute renal failure) would contribute to addressing the physicians' concern about adverse effects of delaying BP lowering drug treatment in individuals without established CVD.

Some previous studies[270-272] showed that individuals with lower treated BP, a smaller number of medications and no history of CVD are likely to maintain 'normal' BP after drug withdrawal for one year or longer. A pragmatic trial[273] showed that deprescribing BP and blood lipid lowering drug treatment in low CVD risk population was safe, as indicated by the slightly increased CVD risk estimation after two years. The Trial of Nonpharmacologic Interventions in the Elderly (TONE)[274] focussed on participants with the above characteristics (BP<145/85 mmHg on one medication and no history of CVD within six months). Kostis et al[274] reported that after successfully withdrawing BP lowering drug treatment, no substantial difference of major CVD event risk was observed over 3-year follow-up between participants randomised to usual care and those randomised either to dietary sodium reduction alone, weight loss alone, or combined sodium reduction and weight loss. However, there was a trend of increasing major CVD events according to increasing age, particularly on those over 70 years old. A similar trial on younger population should be performed to

investigate the effects on 'hard' outcomes such as major CVD events and mortality. A subgroup analysis by absolute CVD risk may be helpful to identify those who could have potential 'harms'.

The association between BP and incidence of dementia is also among the other important concerns. Midlife high BP (systolic BP >140 mmHg) was associated with an increased risk of dementia, however a steep decline of systolic BP during mid-to-late life was also associated with at least two-fold increased risk of dementia[275]. Future studies of BP pharmacological treatment in the middle-aged population could examine further 'benefits' or 'harms' of BP lowering effects on cognitive functions and incidence of dementia.

The research in chapter 5 found a delayed mortality benefit of lipid lowering drug treatment in an observational study, that should be confirmed by an intervention trial. STAREE[276] is an ongoing randomised controlled trial in the 'healthy' elderly of 70 years or over that will merit the 'benefits' or 'risk' of statins (the most commonly-used lipid lowering drug treatment) regarding fatal and non-fatal event over a five year follow-up. STAREE is expected to be completed in the next few years and should timely address the uncertainty of statin treatment in the 'healthy' elderly before widespread use of statins becomes an irreversible trend in clinical practice.

Public health implications

Our research findings encourage the adoption of the absolute risk approach in identifying high CVD risk individuals who are most likely to benefit from the lifetime use of BP and lipid lowering drug treatment as recommended in most current guidelines in Australia, New Zealand, Europe and the US[1, 3, 49, 58]. The adoption of these guidelines should be enhanced in current practice. Indeed, such an approach following the above guidelines has reduced the number of undertreatment cases (normal BP but at high risk), however overtreatment (elevated BP but at low-moderate) exists due to widespread concern about the negative consequences of no treatment. If this is the case, the decision making should be shared with patients in terms of the ambiguous benefits and harms, quality of life, cost of drug treatment and management. Particularly, in the 'healthy' elderly (>65 years), the findings from chapter 5

indicates that mortality benefits of lipid lowering drug treatment may take longer than five years to become evident, life expectancy and polypharmacy burdens should be taken into account.

Conclusions

The findings of this research provide further justifications for the superiority of absolute cardiovascular risk in identifying those who are most likely to benefit from blood pressure and blood lipid lowering drug treatments. No evidence of adverse 'legacy effects' of delayed BP lowering drug treatment emerged in both short- and long-term studies in individuals without established CVD, even in those with high 10-year CVD risk estimation. In contrast, the 'healthy' elderly may have a delayed mortality benefit from lipid lowering drug treatment and the high risk elderly appeared to obtain the benefits earlier.

Appendix

Publications and conference presentations

Publications and conference presentations generated from this thesis are listed in the following:

Articles (Peer-Reviewed):

Ho CLB, Breslin M, Doust J, Reid CM, Nelson MR. (2018). Effectiveness of blood pressure-lowering drug treatment by levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study. BMJ open, 8(3), e017723.

Ho CLB, Sanders S, Doust J, Breslin M, Reid CM, Nelson MR. Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review. JMIR Res Protoc 2017;6(9):e177. DOI: 10.2196/resprot.8362. PMID: 28864428.

Ho CLB, Chowdhury EK, Breslin M, Doust J, Wing LMH & Nelson, MR. Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study. J Clin Lipidol. 2019;13(1):148-155.

Ho CLB, Breslin M, Chowdhury EK, Doust J, Reid CM, Davis BR, Simpson LM, Nelson MR. Lack of a significant legacy effect of baseline blood pressure' treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. J Hypertens 2019 Oct 3. doi: 10.1097/HJH.0000000000002280 [Epub ahead of print]

Conference Proceedings (Peer-Reviewed):

Ho CLB, Doust J, Jackson R, McManus RJ, Reid CM, Sundstrom J, & Nelson, MR (2016). Should You Leave A Legacy? Potential Effects of Delayed Blood Pressure Lowering Pharmacotherapy In Individuals Stratified By Absolute Cardiovascular Disease Risk. In Hypertension (Vol. 67, pp. E17-E18).

Ho CLB, Breslin M, Doust J, Reid CM, Nelson MR. (2017). Post hoc analysis of the effectiveness of blood pressure lowering Drug treatment by levels of absolute risk in the ANBP Study. In Hypertension (Vol. 69, pp. E26)

Conference presentations

Oral

Ho CLB, Breslin M, Doust J, Reid CM, Nelson MR. Post hoc analysis of the effectiveness of blood pressure lowering Drug treatment by levels of absolute risk in the ANBP Study. The 2016 Annual High Blood Pressure Research Council of Australia Meeting, Hobart, 2016.

Ho CLB, Chowdhury EK, Breslin M, Doust J, Reid CM, Nelson MR. Ten-year legacy effect of delayed lipid lowering drug treatment on cardiovascular disease in the Second Australian National Blood Pressure study (ANBP2). The 2017 Annual High Blood Pressure Research Council of Australia Meeting, Melbourne, 2017.

Ho CLB, Chowdhury EK, Breslin M, Doust J, Reid CM, Davis R Barry, Simpson M Lara, Nelson MR. Legacy effects of baseline blood pressure 'treatment naivety' in The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack trial (ALLHAT). The 2018 Annual Royal Australian College of General Practitioners conference, Gold Coast, 2018.

Posters:

Ho CLB, Doust J, Jackson R, McManus RJ, Reid CM, Sundstrom J, Nelson MR. Should You Leave A Legacy? Potential Effects Of Delayed Blood Pressure Lowering Pharmacotherapy In Individuals Stratified By Absolute Cardiovascular Disease Risk. The 2015 Annual High Blood Pressure Research Council of Australia Meeting, Melbourne, 2015.

Ho CLB, Breslin M, Doust J, Reid CM, Nelson MR. Comparison Of The Effectiveness Of Blood Pressure Lowering Drug Treatment By The Absolute Risk Classification. The 2016 Annual Royal Australian College of General Practitioners conference, Perth, 2016.

BMJ Open

Effectiveness of blood pressure-lowering drug treatment by levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study

Chau Le Bao Ho,[1] Monique Breslin,[1] Jenny Doust,[2] Christopher M Reid,[3,4] Mark R Nelson[1,4]

To cite: Ho CLB, Breslin M, Doust J, *et al*. Effectiveness of blood pressure-lowering drug treatment by levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study. *BMJ Open* 2018;**8**:e017723. doi:10.1136/bmjopen-2017-017723

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-017723).

Received 12 May 2017
Revised 7 December 2017
Accepted 30 January 2018

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[2]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
[3]School of Public Health, Curtin University, Perth, Western Australia, Australia
[4]CCRE Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Correspondence to
Dr Chau Le Bao Ho;
chau.ho@utas.edu.au

ABSTRACT

Objectives In many current guidelines, blood pressure (BP)-lowering drug treatment for primary prevention of cardiovascular disease (CVD) is based on absolute risk. However, in clinical practice, therapeutic decisions are often based on BP levels alone. We sought to investigate which approach was superior by conducting a post hoc analysis of the Australian National Blood Pressure (ANBP) cohort, a seminal study establishing the efficacy of BP lowering in 'mild hypertensive' persons.

Design A post hoc subgroup analysis of the ANBP trial results by baseline absolute risk tertile.

Setting and participants 3244 participants aged 35–69 years in a community-based randomised placebo controlled trial of blood pressure-lowering medication.

Interventions Chlorothiazide500 mg versus placebo.

Primary outcome measures All-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).

Results Treatment effects were assessed by HR, absolute risk reduction and number needed to treat. Participants had an average 5-year CVD risk in the intermediate range (10.5±6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle aged (52±8 years). In a subgroup analysis, the relative effects (HR) and absolute effects (absolute risk reduction and number needed to treat) did not statistically differ across the three risk groups except for the absolute benefit in all-cause mortality (p for heterogeneity=0.04). With respect to absolute benefit, drug treatment significantly reduced the number of events in the high-risk group regarding any event with a number needed to treat of 18 (10 to 64), death from any cause with 45 (25 to 196) and major CVD events with 23 (12 to 193).

Conclusion Our analysis confirms that the benefit of treatment was substantial only in the high-risk tertile, reaffirming the rationale of treating elevated blood pressure in the setting of all risk factors rather than in isolation.

Strengths and limitations of this study

- ► Our analysis provides further justification that an absolute risk strategy is superior to management based on the BP level alone in identifying those who are most likely to benefit from therapy.
- ► The statistical power to detect treatment effects was limited in this study, and this is a post hoc subgroup analysis.
- ► Due to the lack of high-density lipoprotein cholesterol (HDLc) in the original data set, the HDLc used in the analyses was imputed from a 1980s national survey. The use of these imputed values is unlikely to greatly affect the risk stratification.

INTRODUCTION

For decades, cardiovascular disease (CVD) has remained the greatest burden of disease in the developed world and now also in the developing world.[1 2] In 2012, CVD was responsible for 17.5 million deaths in the world and more than 20 000 deaths in Australia.[1 3] Noticeably, nearly 50% of deaths from CVD are attributable to high blood pressure (BP), the most common modifiable population risk factor.[4] Drug therapy for primary prevention of CVD is now recommended to be based on absolute CVD risk, where BP-lowering drug treatment is determined by BP level together with other major CVD risk factors (eg, sex, age, total cholesterol, high-density lipoprotein cholesterol (HDLc), diabetes and smoking status) as an integrated score.[5–9] Yet clinicians are reticent to treat systolic BP in those below 140 mmHg at high risk as well as not treating patients at low risk with BP above this threshold. There is a paucity of literature on the effects of lowering BP in low to moderate CVD risk individuals with grade 1 hypertension (systolic BP from 140 mmHg to 159 mmHg and/or diastolic BP from 90 mmHg to 99 mmHg) and some debate regarding its benefit.[10] Guidelines from the US and Europe focus on BP thresholds and

promote early drug treatment due to the potential benefits of earlier intervention and potential adverse effects of delayed intervention.[6–8 11–13] JNC 8[11] recommends initiating drug treatment at the threshold of 150 mmHg systolic BP or 90 mmHg diastolic BP for the general population at 60 years or older. This revised recommendation has caused controversy among clinicians who argue that drug treatments need to be initiated at a lower systolic BP of 140 mmHg, as previously recommended in JNC 7[14]; otherwise, patients are exposed to increased risk.[15–18] Similarly, the 2016 European Society of Cardiology guidelines recommend considering BP-lowering drug treatment when systolic BP is greater than 140 mmHg and/or diastolic BP is greater than 90 mmHg after a reasonable period of time with lifestyle choice.[7] Recently, the Systolic Blood Pressure Intervention (SPRINT) trial[19] reported a significant benefit from intensive treatment to a target BP of 120 mmHg rather than 140 mmHg. However, this benefit was observed in those at high CVD risk without diabetes. In agreement with the findings from the SPRINT trial, guidelines in Australia,[5] New Zealand,[20] UK[8] and Canada[9] recommend BP-lowering medication based on absolute CVD risk, recommending BP-lowering treatment as soon as possible in high CVD risk individuals, but not in the low-risk to moderate-risk population unless BP persistently exceeds 160/100 mmHg.

Other groups[21] have recommended early drug treatment of grade 1 hypertension even in patients at low risk with the exception of patients with grade 1 'isolated' hypertension, based on a meta-analysis by Thomopoulos *et al*[22] and the HOPE-3 study.[23] In contrast, a Cochrane review by Diao *et al*[10] concluded that there was no statistically significant effect of BP treatment in individuals who had grade 1 hypertension. The 2015 Blood Pressure Lowering Treatment Trialists Collaboration[24] (BPLTTC) meta-analysis reported a statistically significant benefit of BP-lowering drug treatment in grade 1 hypertension in terms of stroke and all-cause mortality. However, the effects seen in the BPLTTC analysis could reflect differences in the BPLTTC sample that included participants who had diabetes, had a higher baseline risk and had previously received drug treatment. In another analysis of the BPLTTC individual patient data[25] by absolute CVD risk at baseline showed a continuously increasing benefit with baseline risk.[25] The BPLTTC study, however, included participants who both did and did not have a history of CVD.

Thus, we sought to reanalyse a seminal study used to justify treating individuals with elevated BP to see if stratification by baseline CVD risk would be a superior method for identifying candidates for BP-lowering medication in a treatment-naïve population. In this study, we compared the effectiveness of BP-lowering drug treatment by a post hoc subgroup analysis of the Australian National Blood Pressure (ANBP) study.[26] We restricted the analysis group to individuals with no history of CVD or diabetes and who were naïve to BP-lowering treatment. We selected this historical study because it was placebo controlled and patients in the control arm of the study would not have been taking a BP-lowering medication previously unless they had very high levels of BP. Our aim was to assess which group of individuals classified by absolute risk benefited from active treatment versus placebo for CVD events within this seminal study that underwrote the treatment of elevated BP by BP thresholds.

METHODS

We performed a post hoc analysis of the ANBP study[26]. The study was conducted between 1973 and 1979 and was a multicentre, single-blind randomised controlled trial of 3427 patients that compared the effects of BP-lowering drug therapy between individuals who initially received active treatment (chlorothiazide) and those who received delayed active treatment or no active treatment (placebo). The study intervention remains applicable to current practice as thiazide diuretics (eg, hydrochlorothiazide) are still first-line BP-lowering agents.[5–9] The ANBP study enrolled participants who had not been on treatment for hypertension in the past 3 months and had no history of CVD or diabetes. In the 1970s, 'mild hypertension' was defined as a screening diastolic BP of 95–109 mmHg with a systolic BP lower than 200 mmHg. A total of 3931 eligible participants were initially randomised, then 504 participants were excluded because their BP throughout the study did not meet the criteria for starting drug treatment (entry or follow-up diastolic BP higher than 95 mmHg and/or entry or follow-up systolic BP higher than 200 mmHg). The primary endpoints were all-cause mortality and non-fatal events (non-fatal CVD, congestive cardiac failure, renal failure, hypertensive retinopathy or encephalopathy).[26]

Risk stratification

In this analysis, the baseline absolute CVD risk was calculated according to the 5-year Framingham absolute risk score.[27] The Framingham score was chosen because it is currently recommended in the National Vascular Disease Prevention Alliance (NVDPA) guidelines[5] in Australia. The sample was restricted to 3244 participants who were older than 35 years and was stratified by tertile of estimated 5-year CVD risk score. We also classified participants with very high BP (systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg) or total cholesterol (>7.5 mmol/L) values the highest risk tertile regardless of their risk score, as per the Australian guidelines.[5] The ANBP dataset included all variables required for CVD risk calculation except HDLc. The HDLc value was imputed from the Australian National Heart Foundation risk factor prevalence study as this was near contemporaneous with the ANBP.[28] Mean value of HDLc was categorised by age and sex. In a sensitivity analysis, we stratified the sample by Globorisk score,[29] a CVD risk score that does not require HDLc value and is validated in individuals over 40 years. The equation for the Australian population was obtained by personal contact with the author (Peter Ueda, unpublished data, 2016). This analysis excluded 471 participants younger than 40 years. Less

than 1% of the study participants had data missing for total cholesterol, weight and/or height, and these missing data were managed by multiple imputation using chained equations.

Statistical analysis

All analyses were based on the modified 'intention to treat' principle. We included participants who had withdrawn from the study by their group allocation at randomisation in all analyses. The differences in baseline characteristics between 'active group' and 'placebo group' were tested by analysis of variance test for continuous variables and χ^2 test for categorical variables. Treatment effects were assessed by HR, absolute risk reduction (ARR) and number needed to treat (NNT). The HRs and corresponding 95% CIs were estimated by Cox proportional hazard model after adjusting for clustering of participants within community-based centres and potential risk factors including baseline characteristics. The proportional assumption was checked by the test for interaction of HR with time. ARR and NNT were estimated from Kaplan-Meier curves at the median of follow-up time (4.4 years).[30] Tests for interaction of treatment effect over the subgroups were obtained by the Cox regression model for the HR and a Cochran's Q test for the ARR. The threshold for significance for treatment effect was set at 0.05 for the main analysis and subgroup analysis. Only one subgroup analysis with related outcomes was conducted; thus, multiplicity was not likely to affect our results.

RESULTS

Patient characteristics

Table 1 provides baseline characteristics of the participants stratified by the tertile of CVD risk score. On average, study participants had intermediate 5-year CVD risk as referred in the NVDPA guideline (10.5±6.5) with moderately elevated BP (mean 159/103 mmHg) and were middle aged (52±8). The tertiles had estimated 5-year CVD risks of less than 6.1% (low), 6.1%–17.0% (moderate) and more than 17.0% (high). These values are similar to the thresholds recommended by the Australian NVDPA guideline[5] for low (<10%), moderate (10%–15%) and high risk categorisation (>15%). The distribution of baseline characteristics by treatment assignment was not significantly different except for body mass index (BMI) in the total population, the number of smokers in the low-risk group, systolic BP and BMI in the moderate-risk group.

Approximately one-third of the participants (34.5%) prematurely stopped study treatment due to decisions by clinics, participants' doctors and the participant themselves, or for unknown reasons (table 2). Participants' doctors were more likely to stop placebo treatment in all three risk groups, whereas clinics withdrew more BP-lowering drug-randomised participants in the low-risk group and the high-risk group. No substantial difference in baseline characteristics between the two randomised treatment groups was recorded in any risk group.

Effect of BP-lowering drug treatment on total study population

During a median follow-up of 4.4 years (IQR 1.0–5.9), 257 major CVD events (7.9%) were observed, in which ischaemic heart disease accounted for 203 events (6.3%), stroke accounted for 48 events (1.5%) and congestive heart failure accounted for six events (0.2%).

After adjustment for sex, age, BMI, smoking, systolic BP at baseline and study centres, BP-lowering treatment was associated with a 15% reduction in non-fatal events and a 25% reduction in all-cause mortality (figure 1), although the treatment effects were not statistically significant. Similar effects were found in the secondary endpoints including any events HR 0.82 (0.65–1.03), major CVD events HR 0.83 (0.65–1.07) and non-fatal CVD events HR 0.87 (0.67–1.13). We identified a marginally significant effect in stroke HR 0.55 (0.3–1.001).

Effect of BP-lowering drug treatment on 5-year CVD risk groups

In the subgroup analysis, the magnitude of relative treatment effect increased from low to high CVD risk group,

Table 1 Baseline characteristics stratified by tertile of baseline CVD risk score

Group variable	Total	Low (<6.1%)	Moderate (6.1%–17.0%)	High (>17.0%)
Sample, N	3244	1082	1081	1081
Randomised to active treatment, N (%)	1622 (50%)	559 (51.7%)	513 (47.5)	550 (50.9)
Age, years	51.7±8.1	46.0±6.2	54.5±6.5	54.6±8.1
Male sex, N (%)	2017 (62.2)	567 (52.4)	804 (74.4)	646 (59.8)
Current smoker, N (%)	801 (24.7)	**115 (10.6)**	352 (32.6)	334 (30.9)
SBP, mmHg	159.5±17.5	148.4±12.2	**157.3±12.2**	172.6±17.9
DBP, mmHg	102.9±6.8	100.0±3.8	100.8±4.4	107.9±8.2
Total cholesterol, mmol/L	6.0±1.1	5.5±0.9	6.0±0.9	6.5±1.3
BMI, kg/m^2	**26.6±3.9**	26.6±4.0	**26.5±3.6**	26.7±4.1

Bold values: P<0.05 based on the distribution of baseline characteristics by treatment assignment.
BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Characteristics of those who prematurely stopped study regimen

Group variable	Total	Low (<6.1%)	Moderate (6.1%–17.0%)	High (>17.0%)
Sample, N	1119	404	346	369
Randomised to active treatment, N (%)	531 (47.5)	204 (50.5)	151 (43.6)	176 (47.7)
Age, years	51.2±8.3	45.9±6.4	54.1±7.0	54.2±8.5
Male sex, N (%)	626 (55.9)	188 (46.5)	243 (70.2)	195 (52.9)
Current smoker, N (%)	321 (28.7)	58 (14.4)	143 (41.3)	120 (32.5)
SBP, mmHg	159.1±18.1	147.6±12.9	157.0±11.9	173.7±17.7
DBP, mmHg	102.9±6.8	100.0±4.0	100.6±4.2	108.1±8.2
Total cholesterol, mmol/L	6.0±1.1	5.5±0.9	6.0±0.9	6.4±1.3
BMI, kg/m^2	26.7±4.1	26.7±4.0	26.6±3.9	26.8±4.5
Reason for stopping				
Clinic, N (%)	204 (18.2)	**74 (18.3)**	75 (21.7)	**55 (14.9)**
Local doctor, N (%)	287 (25.7)	**98 (24.3)**	**87 (25.1)**	**102 (27.6)**
Participants, N (%)	548 (49.0)	204 (50.5)	162 (46.8)	182 (49.3)
Not known, N (%)	80 (7.2)	28 (6.9)	22 (6.4)	30 (8.1)

Bold values: P<0.05 based on the distribution of baseline characteristics by treatment assignment.
BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

though the benefits were not statistically significant in the high-risk group in terms of all-cause mortality 0.60 (0.26–1.40) and major CVD event with HR 0.76 (0.52–1.10).

The increasing trend for the benefit was also observed when comparing the absolute treatment effects ARR among the three risk groups. No evidence of heterogeneity was observed except the effect in the major CVD event. Substantial effects of BP-lowering treatment were produced in the high-risk group regarding any trial endpoints (ARR 5.6 (95% CI 1.6 to 9.6)), all-cause mortality (ARR 2.2 (95% CI 0.5 to 3.9)) and any CVD event (4.3 (95% CI 0.5 to 8.1)) (table 3). Treating 18 high-risk participants for 4 years prevented one trial event, treating 45 prevented one death and treating 23 prevented one CVD event. In contrast, treating low or moderate-risk participants needed much higher numbers to prevent one event or possibly caused net harm (table 3). Also, a sensitivity analysis by using the GLOBORISK score,[29] which does not require HDLc, was consistent with our original findings, except that the ARR in major CVD event is no longer statistically significant with ARR 3.4% (−0.4% to 7.3%, P=0.08).

DISCUSSION

In our post hoc analysis of the ANBP study, we found evidence of benefit from BP-lowering treatment in the high-risk tertile for primary trial endpoints of any event and any CVD event with low or moderate-risk participants unlikely to benefit. Our study population had an overall moderate 5-year CVD risk (10.5%) and moderately elevated systolic BP (mean 159/103 mmHg) by modern definitions. The ANBP study aimed to treat 'mild hypertension' (according to the old definition) that

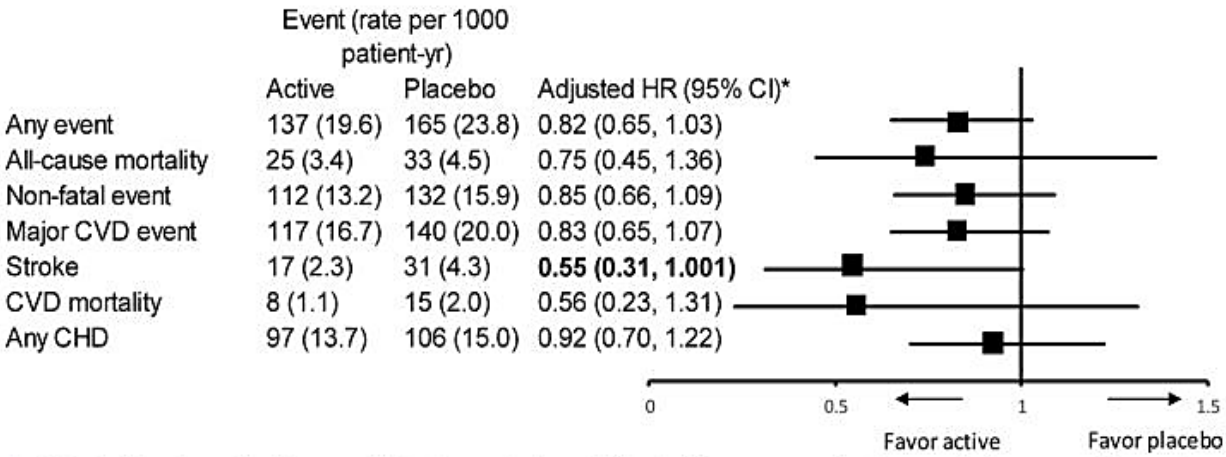


Figure 1 Effect of treatment in the overall study population. *Adjusted for age, sex, body mass index, screening centres, smoking and systolic blood pressure. Bold values: P<0.05. CHD, coronary heart disease; CVD, cardiovascular disease.

Table 3 Effect of treatment by tertile of baseline CVD risk score

	Active placebo		Adjusted HR (95% CI)*	ARR % (95% CI)†	NNT
	Event (rate per 1000 patient-year)				
Any event					
Low	22 (8.9)	23 (10.0)	0.94 (0.52 to 1.70)	−0.3 (−2.7 to 2,1)	−370 (−37 to 47)
Moderate	56 (26.1)	67 (28.0)	0.93 (0.65 to 1.33)	1.1 (−2.9 to 5.2)	87 (−34 to 19)
High	59 (24.8)	75 (33.2)	0.75 (0.53 to 1.06)	**5.6 (1.6 to 9.6)**	**18 (10 to 64)**
P value	–	–	0.64	0.05	–
All-cause mortality					
Low	6 (2.4)	6 (2.5)	0.96 (0.30 to 3.01)	−0.5 (−1.6 to 0.7)	−213 (−63 to 153)
Moderate	10 (4.4)	13 (5.1)	0.81 (0.35 to 1.86)	0.2 (−1.7 to 2.1)	476 (−60 to 48)
High	9 (3.5)	14 (5.7)	0.60 (0.26 to 1.40)	**2.2 (0.5 to 3.9)**	**45 (25 to 196)**
P value	–	–	0.78	**0.04**	–
Non-fatal event					
Low	16 (6.4)	17 (7.4)	0.93 (0.47 to 1.87)	0.2 (−1.9 to 2.3)	476 (−52 to 43)
Moderate	46 (21.3)	54 (22.2)	0.96 (0.65 to 1.43)	0.9 (−2.8 to 4.5)	118 (−35 to 22)
High	50 (20.9)	61 (26.6)	0.80 (0.55 to 1.16)	3.3 (−0.4 to 7.0)	30 (−249 to 14)
P value	–	–	0.77	0.36	–
Major CVD event					
Low	17 (6.8)	18 (7.8)	0.98 (0.50 to 1.91)	0.2 (−1.9 to 2.3)	476 (−52 to 43)
Moderate	50 (23.2)	58 (24.0	0.98 (0.67 to 1.43)	0.6 (−3.2 to 4.5)	164 (−31 to 22)
High	50 (20.9)	64 (28.0)	0.76 (0.52 to 1.10)	**4.3 (0.5 to 8.1)**	**23 (12 to 193)**
P value	–	–	0.62	0.17	–
Any CHD					
Low	17 (6.8)	14 (6.0)	1.21 (0.59 to 2.48)	−0.4 (−2.4 to 1.6)	−256 (−41 to 61)
Moderate	39 (17.9)	47 (19.2)	0.93 (0.60 to 1.42)	1.1 (−3.0 to 5.1)	94 (−33 to 19)
High	41 (17.0)	45 (19.2)	0.90 (0.59 to 1.37)	1.9 (−1.4 to 5.3)	52 (−72 to 19)
P value	–	–	0.83	0.47	–

Bold values: P<0.05.
P value indicated p for interaction.
*Adjusted for age, sex, body mass index, smoking, screening centres and systolic blood pressure.
†As estimated by the Kaplan-Meier curve.
ARR, absolute risk reduction; CHD, coronary heart disease; CVD, cardiovascular disease; NNT, number needed to treat; NNTB, NNT (benefit); NNTH, NNT (harm).

was primarily defined by diastolic BP. Some randomised participants were excluded from the original analysis because they did not meet the criteria for starting BP-lowering drug treatment postrandomisation. This would not be seen in modern clinical trials. In our reanalysis, we found that BP-lowering drug treatment reduced the risk of major CVD events and all-cause mortality, but the effect was not statistically significant. This is likely to be due to reduced power as the cohort was analysed by tertile of absolute risk, as well as by the two groups of randomised therapy. The original study found a statistically significant reduction in the incidence of CVD mortality and all trial endpoints, using the full dataset and a risk ratio (RR) rather than time-to-event analysis.[26]

In our analysis of subgroups defined by CVD risk score, the magnitude of relative treatment effects (relative risk reduction) on all-cause mortality and major CVD events increased across all three CVD risk group from low to high risk, without statistically significant heterogeneity (P=0.78 for all-cause mortality and P=0.62 for the major CVD event) (table 3). All relative treatment effects in our analysis measured by HRs were adjusted by age, sex, BMI, smoking, screening centres and systolic BP. However, no significant difference was observed between adjusted and unadjusted HRs. In terms of absolute benefits, risk reduction linearly increased across the CVD risk group from low to high risk. BP-lowering drug treatment produced an unclear benefit in the low and intermediate CVD risk group but a significant benefit in the high CVD risk group. Heterogeneity of absolute effects across the CVD risk groups was only significant in all-cause mortality (P=0.04).

Regarding the benefit of BP-lowering drug treatment in the low to intermediate CVD risk population, our results

from main and subgroup analyses match well with the study outcomes from the HOPE-3 trial[23] and the Diao review.[10] In the HOPE-3 trial,[23] no benefit of intensive drug treatment was established in the intermediate-risk persons with HR 0.98 (0.84–1.14) for all-cause mortality and HR 0.92 (0.79–1.06) for major CVD events referred as a first secondary outcome in the paper. At baseline, the HOPE-3 participants were older (65 years) and had a lower level of BP (138.1/81.9 mmHg) compared with the ANBP participants. One reason for the lower BPs may be due to the 4-week run-in phase in which all of the HOPE-3 participants received active BP-lowering drug treatment before randomisation, and one-fifth of all eligible participants had previously received drug treatment before the trial. In 2012, Diao *et al* reviewed placebo randomised controlled trials in grade 1 hypertension and also found no beneficial effect of drug treatment with a RR 0.85 (0.63–1.15) for all-cause mortality and RR 0.97 (0.2–1.32) for major CVD events.[10] The participants in the Diao review were likely to have a lower CVD risk than those in the ANBP and the HOPE-3 trials, with major CVD events occurring in only 2.4% of participants in the placebo group. Following a similar approach, in 2015, the BPLTTC[24] reviewed randomised controlled trials in grade 1 hypertension but extended to trials comparing active or more intensive regimens and placebo or less intensive regimens. In line with the findings from the 2015 BPLTTC study, we identified a marginally significant effect on stroke, yet our effect estimates with an HR 0.75 (0.45–1.36) for total deaths and an HR 0.83 (0.65–1.07) for major CVD events slightly differed from the 2015 BPLTTC study's results with an OR 0.78 (0.67–0.92) and an OR 0.86 (0.74–1.01) correspondingly. The differences in CIs may be due to the difference in sample sizes and baseline characteristics. It is more likely that the 2015 BPLTTC participants had higher CVD risk and higher BP value at baseline when about 40% of 15 266 participants had diabetes and about 23% had previously received BP-lowering drug treatment. Our study and the 2015 review confirm the absolute benefits of BP-lowering drug treatment in high CVD risk population in terms of total deaths with ARR 2.2% (0.5% to 3.9%, P=0.01) for the ANBP and ARR 1.4% (0.5% to 2.2%) for the review. Furthermore, the benefit was also recorded in major CVD event with ARR 4.3% (0.5% to 8.1%, P=0.03) in the ANBP, whereas the 2015 BPLTTC observed a non-significant effect with ARR 1.0% (−0.1% to 1.9%). The difference can be explained in part by the study design when more than 50% of participants with systolic BP higher than 160 mmHg in eligible studies in the 2015 BPLTTC were excluded. The distribution of these excluded participants might not be even between active arm and control arm, thus biasing the treatment effects.

In another subgroup analysis stratified by tertile of baseline systolic BP (online supplement), the mean value of CVD risk varied from low to high corresponding to the lowest and the highest tertile. The relative treatment benefits were not statistically significant, but in terms of absolute effects, BP-lowering drug treatment substantially reduced any trial events, all-cause mortality and major CVD events within the highest tertile. The findings were in line with what we found in the CVD risk-stratified subgroup when all participants in the highest BP-stratified tertile had high CVD risk score (20.7±9.5). However, the heterogeneity of treatment effects among the three subgroups in analysis by baseline systolic BP was no longer significant as it was in the subgroup analysis by CVD risk score. Furthermore, the trend of lower to higher absolute benefit from low-risk to high-risk groups that was seen for CVD risk was not apparent when groups are defined by BP alone. Thus, in this study, CVD risk score identified those who most benefited from BP-lowering drug treatment.

Limitations

There are a number of limitations of our study. First, statistical power is unavoidably decreased in a post hoc subgroup analysis, and the multivariate Framingham risk score used in our analysis has not been well validated within the Australian population.[31] However, using a multivariate score for stratification is known to increase the power to detect heterogeneity in absolute risk benefit over subgroup analyses that are based on individual risk factors.[32] A prospective study to address the issue of whether there is an advantage in treating BP by absolute risk is unlikely to be performed, because of the very large sample size and very long follow-up time required, particularly in patients at low risk. Therefore, reanalysis of the early placebo-controlled trials seems to be the most feasible approach for assessing the effects of delayed versus early drug treatment in individuals with varying CVD risk together and elevated BP.

Second, the estimation of HDLc from the 1980s national survey may alter the CVD risk score, but we do not believe this method greatly affected the risk stratification because a 0.4 difference in the HDL estimate only results in a 0.01 difference in CVD risk score. Furthermore, no association between HDLc and BP has been observed.[33 34] The sensitivity analysis using Globorisk score[29] without HDLc showed similar results as our main analysis. Although the ARR is no longer statistically significant, this result is likely due to the smaller sample size and subsequent number of events. In conclusion, the sensitivity analysis supports our main analysis.

Third, the paucity of trial endpoints in each CVD risk group prevented us from comparing the effects in some specific outcomes with respect to stroke and deaths from CVD. In addition, approximately one-third of the participants prematurely stopped randomised drug treatment. However, this pattern likely reflects the typical situation to occur in actual clinical practice, and this analysis is conducted on an intention-to-treat basis, so any difference in the estimate of treatment effect due to non-adherence is deliberately retained. Most participants were followed throughout the trial, except those with an unknown reason for stopping: loss to follow-up (7.2%). An analysis with further adjustment by variable

'premature stopped study treatment' did not substantially change our findings, except effects on stroke in general population became statistically significant (0.55, 95% CI 0.30 to 0.99, P=0.05). This is because non-adherence is balanced between the allocated treatment groups.

In conclusion, our research has demonstrated that drug treatment in patients with elevated BP is best directed to those at high risk of incident CVD events. This reinforces the guidelines recommendation to treat based on absolute (or global) CVD risk, rather than according to BP thresholds alone.[5–9]

Acknowledgements In the current study, the researchers gratefully acknowledge the RACGP Foundation and Therapeutic Guidelines Ltd for their support of this project.

Contributors MRN is responsible for the study conception and data archive from the Australian Data Archive. CLBH performed the analysis and drafted the manuscript. MB, CMR and JD provided substantial support on statistical analyses. All authors made great contribution to the interpretation of data, critically revised the manuscript and approved the final version.

Funding The ANBP was supported by the National Health and Medical Research Council of Australia, the Life Insurance Medical Research Fund of Australia and New Zealand, the Victorian Government, the Clive and Vera Ramaciotti Foundations and the Raine Medical Research Foundation of Western Australia.

Competing interests CLBH is a PhD candidate at Menzies Institute for Medical Research; she has received a PhD scholarship from Merle Weaver Postgraduate Scholarship. JD is supported by National Health and Medical Research Council Screening and Test Evaluation Program Grant 633003. CMR is supported by a National Health and Medical Research Council Senior Research Fellowship (1045862). MRN has in the last 5 years served on an advisory board for AMGEN.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015252).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. World Health Organisation. The top 10 causes of death. http://www.who.int/mediacentre/factsheets/fs310/en/ (accessed 13 Nov 2015).
2. Australian Bureau of Statistics. Causes of death, Australia, 2013. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001 (accessed 30 Nov 2016).
3. Australia Bureau of Statistics. Causes of death, Australia, 2012. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012 (accessed 13 Nov 2015).
4. World Health Organisation (WHO). A global brief on hypertension: silent killer, global public health crissis. http://www.thehealthwell.info/node/466541 (accessed 13 Nov 2015).
5. National Vascular Disease Prevention Allianace. Guidelines for the management of absolute cardiovascular disease risk. http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27.Updated (accessed 13 Nov 2015).
6. Task Force for the management of arterial hypertension of the European Society of HypertensionTask Force for the management of arterial hypertension of the European Society of Cardiology. 2013 ESH/ESC guidelines for the management of arterial hypertension. *Blood Press* 2013;22:193–278.
7. Piepoli MF, Hoes AW, Agewall S, *et al*. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.
8. Krause T, Lovibond K, Caulfield M, *et al*. Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.
9. Dasgupta K, Quinn RR, Zarnke KB, *et al*. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2014;30:485–501.
10. Diao D, Wright J, Cundiff D, *et al*. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012;15:CD006742.
11. James PA, Oparil S, Carter BL, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 20142014;311:507–20.
12. Whitworth JA. World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983–92.
13. Weber MA, Schiffrin EL, White WB, *et al*. Clinical practice guidelines for the management of hypertension in the community. *J Clin Hypertens* 2014;16:14–26.
14. Chobanian AV, Bakris GL, Black HR, *et al*. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206–52.
15. Mitka M. Groups spar over new hypertension guidelines. *JAMA* 2014;311:663–4.
16. Guallar E, Laine C. Controversy over clinical guidelines: listen to the evidence, not the noise. *Ann Intern Med* 2014;160:361–2.
17. Wright JT, Fine LJ, Lackland DT, *et al*. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. *Ann Intern Med* 2014;160:499–503.
18. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? *J Hypertens* 2009;27:1509–20.
19. Wright JT, Williamson JD, Whelton PK, *et al*. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103–16.
20. New Zealand Guidelines Group. *The assessment and management of cardiovascular risk*. Wellington: New Zealand Guidelines Group. http://www.health.govt.nz/publication/assessment-and-management-cardiovascular-risk (accessed 13 Nov 2015).
21. Morales Salinas A, Coca A, Olsen MH, *et al*. Clinical perspective on antihypertensive drug treatment in adults with grade 1 hypertension and low-to-moderate cardiovascular risk: an international expert consultation. *Curr Probl Cardiol* 2017;42:198–225.
22. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. *J Hypertens* 2014;32:2296–304.
23. Lonn EM, Bosch J, López-Jaramillo P, *et al*. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009–20.
24. Sundström J, Arima H, Jackson R, *et al*. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. *Ann Intern Med* 2015;162:184–91.
25. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;384:591–8.
26. The Australian therapeutic trial in mild hypertension. Report by the management committee. *Lancet* 1980;1:1261–7.
27. Anderson KM, Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.
28. Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results from the National heart foundation's risk factor prevalence study, 1980-1989. *Med J Aust* 1994;161:519–27.
29. Hajifathalian K, Ueda P, Lu Y, *et al*. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a

pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol* 2015;3:339–55.
30. Bender R, Kromp M, Kiefer C, *et al*. Absolute risks rather than incidence rates should be used to estimate the number needed to treat from time-to-event data. *J Clin Epidemiol* 2013;66:1038–44.
31. Zomer E, Owen A, Magliano DJ, *et al*. Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the 'old' versus the 'new' Framingham equation. *Eur J Cardiovasc Prev Rehabil* 2011;18:115–20.
32. Hayward RA, Kent DM, Vijan S, *et al*. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. *BMC Med Res Methodol* 2006;6:1.
33. Hughes K, Leong WP, Sothy SP, *et al*. Relationships between cigarette smoking, blood pressure and serum lipids in the Singapore general population. *Int J Epidemiol* 1993;22:637–43.
34. Catalano M, Aronica A, Carzaniga G, *et al*. Serum lipids and apolipoproteins in patients with essential hypertension. *Atherosclerosis* 1991;87:17–22.

BMJ Open

Effectiveness of blood pressure-lowering drug treatment by levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study

Chau Le Bao Ho, Monique Breslin, Jenny Doust, Christopher M Reid and Mark R Nelson

*BMJ Open*2018 8:
doi: 10.1136/bmjopen-2017-017723

Abstracts From the 37th Annual Scientific Meeting of the High Blood Pressure Research Council of Australia

Melbourne, Australia
December 2-4, 2015
Editor: Brian J. Morris

Publication supported by

SERVIER

transducing device inserted at least 10 days prior to timed mating. The remaining animals (control n=3; PLGF-2 n=3) were subject to multi-slice multi-echo magnetic resonance imaging in an 11.74 Tesla spectrometer on gd 17. Animals were euthanized at gd 17 and plasma, urine and tissue were collected for analysis. Data was expressed as mean±SEM.
Results: There was no difference in blood pressure or proteinuria (648±231 vs. 506±74 mg/mmol; *P*=0.59) between mice receiving control or PLGF-2. Serum FLT-1/PLGF ratio was significantly higher in mice administered PLGF-2 (333±18.6 vs. 493±44.6; *P*=0.007). There was also no observed difference in T2 labyrinthine/junctional zone ratio (*P*=0.59) in mouse placentas imaged (controL, 2.29±0.11, n=18, vs. PLGF, 2.22±0.11 n=16).
Conclusions: PLGF-2 does not ameliorate features of experimental preeclampsia induced by TNF-alpha infusion. Contrary to expectations, serum FLT-1/PLGF ratio rises with PLGF-2 treatment suggesting a potentially unfavourable effect of supra-physiological levels of PLGF prior to development of preeclampsia.

PREDICTIVE PERFORMANCE OF ECHOCARDIOGRAPHIC PARAMETERS FOR CARDIOVASCULAR EVENTS AMONG ELDERLY TREATED HYPERTENSIVE PATIENTS

Chowdhury EK[a], Jennings G[b], Dewar E[b], Wing LMH[c], Reid CM[a,d] on behalf of the ANBP2 Management Committee

[a]Centre of Cardiovascular Research & Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [b]Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia; [c]School of Medicine, Flinders University, South Australia, Australia; [d]School of Public Health, Curtin University, Perth, Western Australia, Australia

Background: Hypertension leads to cardiac structural and functional changes, commonly assessed by echocardiography. It is not clear which echocardiographic parameters are most predictive of future cardiovascular events among elderly treated hypertensive patients over the short or long term.
Aim: To assess the predictive performance of different echocardiographic parameters in relation to cardiovascular outcomes in elderly hypertensive patients.
Methods: Echocardiographic data from the Second Australian National Blood Pressure study were used. Participants aged ≥65 years at enrolment were followed for cardiovascular events and mortality for a median of 4.1 years (short-term) and then a further median of 6.9 years (long-term). Echocardiograms were performed at baseline to measure direct and derived parameters. Left ventricular hypertrophy (LVH) was defined using threshold values of left ventricular mass (LVM) indexed to either body surface area (BSA) or height$^{2.7}$: >115/95 g/m^2 or ≥49/45 g/m$^{2.7}$ (in males and females, respectively) and ≥125 g/m^2 or ≥51 g/m$^{2.7}$ (for both sexes).
Results: The prevalence of LVH ranged from 33–70% among the study participants (n=679) at baseline depending on the threshold used to define LVH. Of the echocardiographic parameters, after adjusting for potential risk factors using Cox-regression proportional hazard models, only LVH defined using LVMI-BSA (>115/95 g/m^2) predicted cardiovascular events and mortality over the short and long-term. Participants having LVH at baseline had twice the risk (hazard ratio, 95% confidence interval) of having any first cardiovascular event over the short-term (1.96, 1.11–3.45; *P*=0.02); and any fatal cardiovascular events (1.96, 1.14–3.37; *P*=0.02) over the long-term. Among other echocardiographic parameters, LV wall thickness, LV mass, and systolic dysfunction (i.e., abnormal fractional shortening) predicted only short-term cardiovascular events.
Conclusions: In elderly treated hypertensive patients LVH identified by echocardiography based on LVM indexed to BSA (>115/95 g/m^2) was a reliable predictor of future cardiovascular events and mortality.

CENTRAL-TO-BRACHIAL BLOOD PRESSURE AMPLIFICATION IN PATIENTS TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF NON-INVASIVE MEASUREMENT

Climie RED[a], Otahal P[a], Schultz MG[a], Fell JW[b], Srikanth V[c], Sharman JE.[a]

[a]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; [b]School of Human Life Sciences, University of Tasmania, Launceston, Tasmania, Australia; [c]Stroke and Ageing Research Group, Monash Medical Centre, Department of Medicine, Southern Clinical School, Monash University, Melbourne, Victoria, Australia

Background: Brachial blood pressure (BP) may not reflect central BP due to systolic BP (SBP) amplification. Patients with type 2 diabetes mellitus (T2DM) elicit vascular irregularities that may affect SBP amplification or other central BP indices (including pulse pressure [PP], augmentation pressure [AP] and augmentation index [AIx]), but this has never been systematically assessed by comparison to individuals without T2DM.
Aim: To determine, by systematic review and meta-analysis, the magnitude and variation of central-to-brachial SBP and PP amplification, AIx and AP in patients with T2DM compared to those without.
Methods: Six online databases were searched for published studies reporting non-invasive central and brachial SBP in those with and those without T2DM. Random effects meta-analyses and meta-regression were used to analyse the studies.
Results: We identified 17 studies with a total of 2,711 patients with T2DM and 10,460 controls without T2DM. There was no significant difference in SBP amplification between groups (T2DM=10.8 mmHg, no T2DM=10.2 mmHg; pooled estimate = 0.6mmHg (95% CI –0.3 and 1.5, respectively; *P*=0.21), but there was a large variation in both (T2DM range = 2.0–16.6 mmHg, non-diabetic range = 1.0–16.1 mmHg). In the meta-regression, duration of T2DM explained 16.3% of the variance in the pooled data (*P*=0.15). The difference in amplification between groups increasing by 0.3 mmHg per year of T2DM. PP amplification was not significantly different between groups (*P*=0.16). AP, AIx and AIx corrected for heart rate were significantly higher in T2DM (*P*<0.05 for all).
Conclusions: Patients with T2DM have increased AP and AIx, but no difference in SBP (or PP) amplification, compared to those without T2DM. However, SBP amplification is highly variable and increases with duration of T2DM; altogether confirming that central systolic loading cannot be assessed from brachial BP in patients with T2DM.

BLOOD PRESSURE RESPONSE TO RENAL DENERVATION IN PATIENTS WITH RESISTANT HYPERTENSION AND MULTIPLE RENAL ARTERIES

Hering D[a,b], Marusic P[a,b], Walton AS,[c] Duval J[a], Head G[d], Esler MD[c], Schlaich MP[a,b]

[a]Neurovascular Hypertension & Kidney Disease Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Victoria, Australia; [b]School of Medicine and Pharmacology – Royal Perth Hospital Unit, University of Western Australia, Perth, Western Australia, Australia; [c]Heart Centre Alfred Hospital, Melbourne, Victoria, Australia; [d]Neuropharmacology Laboratory, Baker IDI Heart & Diabetes Institute, Melbourne, Victoria, Australia

Background: Renal denervation (RDN) has been demonstrated to lower blood pressure (BP) and muscle sympathetic nerve activity (MSNA) in patients with resistant hypertension (RH). Previous studies have predominantly included patients with single renal arteries bilaterally. Whether RDN is feasible, safe and effective in patients with multiple renal arteries or variable renal artery anatomy remains obscure.
Aim: To determine the efficacy of RDN in patients with RH and multiple renal arteries.
Methods: We measured 24-hour BP at baseline, 3 and 6 months after RDN in 91 patients with RH including 65 patients with single renal arteries bilaterally (Group 1), 16 patients with dual renal arteries on either one or both sides (Group 2), and 10 patients with other anatomical constellations or structural abnormalities (Group 3). MSNA was obtained in 39 out of 91 patients at baseline and follow-up.
Results: RDN significantly reduced daytime SBP in group 1 from 152±17 mmHg at baseline to 145±14 mmHg at both 3 and 6 months follow-up (*P*<0.001), but not in group 2: 149±12 mmHg at baseline vs. 144±16 mmHg at 3 and 6 months follow up (*P*=0.32); nor in group 3: 156±17 mmHg at baseline vs. 154±19 mmHg at 3 and 146±13 mmHg at 6 months follow-up (*P*=0.13). Resting baseline MSNA was only reduced in group 1, from 51±14 bursts/min at baseline to 45±17 bursts/min at 3 and 43±14 bursts/min at 6 months post procedure (*P*<0.05). There was no deterioration in kidney function in either group.
Conclusions: RDN can be performed safely in patients with RH irrespective of renal artery anatomy. The presence of single renal arteries with or without structural abnormalities is associated with a more pronounced RDN-induced reduction in BP and MSNA when compared to the presence of dual renal arteries. However, when patients with dual renal arteries underwent renal nerve ablation in all existing arteries, a greater BP reduction was observed suggesting that incomplete renal sympathetic denervation may account for differing BP responses.

SHOULD YOU LEAVE A LEGACY? POTENTIAL EFFECTS OF DELAYED BLOOD PRESSURE LOWERING PHARMACOTHERAPY IN INDIVIDUALS STRATIFIED BY ABSOLUTE CARDIOVASCULAR DISEASE RISK

Ho CLB[a], Doust J[b], Jackson R[c], McManus RJ[d], Reid CM[e,f], Sundström J[g], Nelson MR[a]

[a]University of Tasmania, Hobart, Tasmania, Australia; [b]Bond University, Gold Coast, Queensland, Australia; [c]University of Auckland, Aukland, New Zealand; [d]Oxford University, UK; [e]Monash University, Clayton, Victoria, Australia; [f]Curtin University, Perth, Western Australia, Australia; [g]Uppsala University Hospital, Stockholm, Sweden

Background: Cardiovascular disease (CVD) is still the major contributor to the global burden of disease. To ensure that medication is received by those most likely to benefit from it in primary prevention, the CVD absolute risk approach has been adopted in Australia. However, this approach has become a matter of concern among clinicians who hesitate at adopting a treatment threshold based on an the absolute risk of an individual and that based on the traditional individual risk factor of blood pressure (BP). Updated guidelines do not routinely recommend BP lowering drug therapy in a low absolute CVD risk population (a risk of a CVD event of less than 10% in the next five years) unless a systolic BP threshold of 160 mmHg is exceeded. Many GPs have expressed a concern that delaying pharmacotherapy may lead to irreversible target organ damage, a so called "legacy effect." It is therefore timely to conduct a study addressing the question of whether earlier active BP lowering pharmacotherapy brings therapeutic benefits for a low risk population over their lifetime.
Aim: To investigate the effects of delayed BP lowering therapy on those with elevated BP over a spectrum of absolute risk (low [<10%], medium [10–15%] and high [>15%]) on all-cause and disease-specific mortality.
Methods: We will conduct a post-hoc analysis of long-term CVD mortality and all-cause mortality in the Australian National Blood Pressure study (ANBP). The ANBP study was conducted in the 1970s on 3,427 participants aged 30–69 years who were recruited from the general population with mildly elevated BP and no history of CVD or diabetes. We plan to probability match all participants to the Australia Institute of Health and Welfare National Death Index,

and classify the cause of death by the International Classification of Disease version 10. All analyses will be based on the "intention to treat" principle. Cox proportional hazard models will be used to estimate hazard ratios and corresponding 95% confidence intervals.
Results: To date we have retrieved ANBP study archives and received funding from the Royal Australian College of General Practitioners Research Foundation. An ethics application is being prepared. Interim results will be presented if available.
Conclusion: The present findings might contribute to increasing the adoption of current guidelines into clinical practice by addressing clinician concerns. Such an approach has the potential to significantly reduce the number of well, symptom-free, individuals labeled as having a disease (hypertension) with attendant financial burdens (cost of drugs, monitoring and follow-up) and potential side effects.

KIDNEY TARGETED microRNA-181A MIMIC TREATMENT IN HYPERTENSIVE BPH/2J MICE

Jackson KL[a], Marques FZ[a], Stevenson ER[a], Charchar FJ[b], Davern PJ[a], Head GA[a]

[a]Neuropharmacology Laboratory, Baker IDI Heart and Diabetes Research Institute, Melbourne, Victoria, Australia; [b]School of Health Sciences, Federation University of Australia, Ballarat, Victoria, Australia

Background: BPH/2J mice are a genetic model of hypertension driven by greater activity of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS). During the dark period of the 24-hour light cycle when hypertension is at its greatest, BPH/2J mice display enhanced renal renin mRNA, possibly related to lower levels of microRNA (miR)-181a, which is a negative regulator of renin mRNA.
Aim: To determine whether lower renal miR-181a abundance contributes to elevated RAS activity and hypertension in BPH/2J mice.
Methods: BPH/2J and normotensive BPN/3J control mice (n=6–10) were administered mirVana miR-181a mimic or vehicle as negative control (0, 1, 5 and 25 nmol, i.v) using an *in vivo* kidney-specific transfection reagent (Altogen). Blood pressure (BP) was measured before and for two days following treatment via pre-implanted radiotelemetry probes. The BP response to angiotensin converting enzyme (ACE) inhibition (enalaprilat) and ganglion blockade (pentolinium) was determined during the dark period ~26 h after a 25 nmol dose and kidney tissue was collected at ~50 hours for measurement of renin mRNA.
Results: The peak hypotensive effect of the mimic relative to vehicle treatment in BPH/2J mice was observed 12–15 h after the 5 nmol dose (–5.8±1.5 mmHg), which was greater than the effect in BPH/2J mice treated with the negative control (0.7±1.0 mmHg; P=0.02). However, the effect of the 1 and 25 nmol doses of mimic on BP were comparable between strains and with the negative control (vehicle treatment) (P>0.12). Renal renin mRNA abundance in BPH/2J mice treated with the miR-181a mimic was lower than BPH/2J mice treated with the negative control (3.5±0.6 vs. 4.8±1.1; P=0.01), suggesting that the mimic effectively inhibited renin mRNA *in vivo*. By contrast renin mRNA was comparable in BPN/3J mice treated with either the mimic or negative control, respectively (3.1±0.7 vs. 2.6±0.7; P=0.45). Furthermore the depressor response to enalaprilat in BPH/2J mice treated with the negative control was abolished in BPH/2J mice treated with the mimic (–17±3 mmHg vs. 1±3 mmHg, respectively; P<0.001), suggesting the mimic reduced the RAS contribution to BP maintenance. The depressor response to pentolinium following enalaprilat pre-treatment was comparable between negative control and mimic-treated BPH/2J mice (–52±5 vs. -51±3 mmHg; P=0.80), suggesting the mimic does not overtly affect the SNS contribution to BP in BPH/2J mice.
Conclusion: The present findings provide the first *in vivo* evidence that low miR-181a levels contribute to greater renal renin mRNA level and thereby a contribution of the RAS to the hypertension in BPH/2J mice.

THE EFFECTS OF 8 WEEKS OF INTERVAL SPRINTING EXERCISE ON CARDIOVASCULAR FUNCTION OF OVERWEIGHT POSTMENOPAUSAL WOMEN

Liu D, Lin CP, Boutcher SH, Boutcher YN

School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia

Background: The effect of interval sprinting exercise (ISE) on cardiovascular function of overweight postmenopausal women has not been determined.
Aim: To determine the effect of an 8-week ISE intervention consisting of three weekly 20-min bouts of ISE on cardiac autonomic function.
Methods: Twenty postmenopausal women (BMI 28.8±0.89 kg/m^2; age 53.3±1.3 years) were randomly assigned to an ISE or a control group. Participants underwent pre- and post-training testing including an aerobic fitness test and heart rate and blood pressure variability analysis to measure autonomic influence on the heart. ISE participants undertook 24 supervised exercise sessions that involved 8 s sprinting on a cycle ergometer followed by 12 s of easy pedalling, repeated for a total of 20 minutes.
Results: ISE compared to control women significantly (P<0.05) improved their aerobic fitness (2.33±0.11 vs. 1.79±0.11 L/min). Baroreceptor sensitivity of the ISE (9.35±0.81 ms/mmHg) increased significantly at post-test (P<0.05) compared to the control group (6.96±0.69 ms/mmHg).
Conclusion: Twenty minute bouts of ISE repeated over 24 sessions led to a significant improvement in aerobic fitness and a significant increase in baroreceptor sensitivity.

THE EFFECT OF GENES INVOLVED IN MONOGENIC HUMAN CARDIOMYOPATHIES IN A POLYGENIC MODEL OF CARDIAC HYPERTROPHY

Prestes PR[a], Marques FZ[b], Curl CL[c], Lewandowski P[d], Delbridge LMD[c], Charchar FJ[a], Harrap SB[c]

[a]School of Applied and Biomedical Sciences, Faculty of Science and Technology, Federation University Australia, Ballarat, Victoria, Australia; [b]Heart Failure Research Group, Baker IDI Heart and Diabetes Research Institute, Melbourne, Victoria, Australia; [c]Department of Physiology, University of Melbourne, Melbourne, Victoria, Australia; [d]School of Medicine, Deakin University, Waurn Ponds, Victoria, Australia

Background: Cardiac hypertrophy (CH) is the main risk factor for heart disease after a certain age. We wondered whether genes implicated in monogenic forms of human CH might also be involved in the more common polygenic forms of the disease.
Aim: To use the hypertrophic heart rat (HHR), a unique normotensive polygenic model of CH, to investigate mRNA expression of genes associated with monogenic forms of dilated and hypertrophic cardiomyopathy in humans.
Methods: We measured the expression of 37 transcripts with the TruSeq Targeted RNA expression kit using the MiSeq Desktop sequencer (Illumina) in left ventricles of HHR and its matched control strain, the normal heart rat (NHR), at five ages (2 days old, 4-, 13-, 33- and 50-weeks old).
Results: We found only one gene (*Ttr*) was differentially expressed in all age groups (FDR<0.1; P<0.05). *Ttr* is involved in cardiac amyloidosis, infiltrating cardiovascular structures, leading to hypertrophy. In rats older than 13 weeks old, we found expression of 4 genes (*Actc1, Ankrd1, Cav3 and Fhl2*) was upregulated in the HHR. The proteins encoded by these genes are involved in a variety of muscle development pathways, growth and contractility. Interestingly, *Ankrd1* (fold change 1.3–2.5) has been found to be upregulated in the failing myocardium of dogs and in the left ventricles of patients with CH. *Fhl2* is associated with cardiomyopathy in rats, but seems to not be essential for cardiac development in mice.
Conclusion: Our results show that genes involved in monogenic forms of human CH may also influence polygenic forms of the disease and thus merit further investigation.

BARORECEPTOR SENSITIVITY IN DIABETIC RATS WITH TREATED AND UNTREATED HYPERTENSION

Ramachandran H[a], Salum E[b], Kampus P[b], Kals J[b], Town G[a], Avolio AP[c], Butlin M[c]

[a]Faculty of Engineering, Macquarie University, Sydney, New South Wales, Australia; [b]Department of Cardiology, University of Tartu, Tartu, Estonia; [c]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia

Background: Diabetes is associated with raised blood pressure (BP) and cardiovascular risk. Baroreceptor sensitivity (BRS) is a feedback mechanism controlling spontaneous changes in BP and decreases with age and in different diseases.
Aim: To quantify BRS through spontaneous changes in BP in diabetic rats and rats treated with antihypertensive therapy.
Methods: Male Wistar rats (aged 6 weeks) were divided into control (n=6), control with antihypertensive treatment (control+Tx, telmisartan, 10 mg/kg/day; n=5), induced diabetes (intraperitoneal streptozotocin, 50 mg/kg, confirmed by blood glucose measurement, n=8), and diabetes with antihypertensive treatment (diabetes+Tx; n=8). At 18 weeks, rats were anesthetized (urethane, 1.3 g/kg) and an electrocardiogram performed and aortic BP was measured (1.2 F solid-state pressure tipped catheter, introduced via the femoral artery). BRS was quantified using custom-written scripts to detect sequences of at least 3 pulses with a minimum systolic BP change of 1 mmHg and minimum R-R change of 1 ms.
Results: Both control (142±16 mmHg) and diabetic (132±22 mmHg) rats were hypertensive. Anti-hypertensive treatment successfully lowered systolic BP (control+Tx 105±11 mmHg; diabetes+Tx 119±14 mmHg). Antihypertensive treatment did not alter BRS for either controls (0.87±0.45 ms/mmHg vs. control+Tx 0.88±0.33 ms/mmHg; P=0.95) or diabetic rats (diabetes 1.25±0.29 ms/mmHg vs. diabetes+Tx 1.48±1.04 ms/mmHg; P=0.56). There was also no difference between diabetic rats and controls (P=0.08) or those with antihypertensive treatment (P=0.25).
Conclusions: Despite altering BP through antihypertensive treatment, BRS measured through spontaneous changes in BP, was unchanged for both control and diabetic animals.

INHIBITING MITOCHONDRIAL FISSION WITH MDIVI-1 IMPROVES SURVIVAL OF HUMAN CARDIAC RESIDENT STEM CELLS

Rosdah AA[a,b], Sivakumaran P[a], Delbridge LMD[b], Lim SY[a,c]

[a]O'Brien Institute Department, St. Vincent's Institute, Melbourne, Victoria, Australia; [b]Department of Physiology, University of Melbourne, Melbourne, Victoria, Australia; [c]Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia

Background: Stem cell therapy is a promising approach to treat myocardial infarction. However, survival of transplanted cells is poor due to the hostile environment of the infarcted heart. Therefore, novel strategies are needed to improve the survival of stem cells post-transplantation. Mitochondria are morphologically dynamic organelles constantly undergoing

Abstracts From the 38th Annual Scientific Meeting of the High Blood Pressure Research Council of Australia

Hobart, Australia
December 7–10, 2016
Editor: Brian J. Morris

Publication supported by

SERVIER

macrophages in spleen and kidney of both male and female C57Bl6 mice were found to express GPER intracellularly.
Conclusion: Aldosterone/salt-induced hypertension is lymphocyte-dependent and is attenuated/delayed in females due to GPER activity. Therapeutic activation of GPER, likely on T and/or B cells, exerts antihypertensive effects during hypertension caused by aldosterone/salt but not angiotensin II.

CONSTRUCTING HUMAN CARDIAC TISSUE FROM PLURIPOTENT STEM CELLS INCLUDING ELECTRICAL STIMULATION

Dusting GJ[abc], Hernandez D[ab], Sivakumaran P[a], Shepherd RK[bd], Wong Raymond CB[bc], Pebay A[bc], Lim SY[ab]

[a]O'Brien Institute Department, St Vincents Institute, Melbourne, Victoria, Australia; [b]Departments of Surgery, Medicine, Medical Bionics and Ophthalmology; [c]Centre for Eye Research Australia; [d]Bionics Institute, University of Melbourne, Melbourne, Victoria, Australia

Background: Cardiac tissue engineering, particularly that utilizing autologous human stem cells, has the potential to produce constructs of cardiac tissue for surgical replacement of inefficient or damaged cardiac muscle or pacemaker tissue. Both pediatric and adult applications may be possible. Such constructs will also be useful as testing platforms for development of new drugs and pharmacological safety. We have established platforms to grow robust cardiac constructs with an integrated vasculature, constructs that grow and survive transplantation. Fully vascularized, robust beating cardiac tissue has been grown in pedicles constructed in polyacrylate chambers, and implanted *in vivo* in rats.
Aim: To grow integrated constructs of human cardiac tissue of mature ventricular phenotype from stem cells.
Methods: We have used both mesenchymal stem cells (MSC) and induced pluripotent stem (iPS) cells as sources of human cardiomyocytes to grow cardiac constructs *in vivo*. Using the traditional embryoid body (EB) approach to generate beating, cardiomyocyte-like cells from iPS cells, we stimulated these differentiating cells electrically in bespoke chambers for short periods of up to 15 min. In a separate series of experiments, iPS cells were grown in monolayers, replated into the stimulating chambers for 4 d then stimulated continuously (1 ms, 200 mV/mm, 1Hz) for 7 d. Finally other iPS-derived cells grown in monolayers were replated into a fibrin matrix (>l.5 million cells per batch), then implanted into specially designed polyacrylate chambers incorporating miniaturized power packs and stimulating electrodes. These cell batches were wrapped around arterial and venous femoral vessels, implanted *in vivo* in immunocompromised rats, and stimulated for 4 h daily for 3 weeks, using a cage with pulsating orthogonal magnetic field, which generated charge-balanced electrical pulses in the chamber with the same parameters as those previously used *in vitro*. The tissues thus produced were examined after 3 weeks of stimulation in one leg, the tissues growing in the other with similar chambers that lacked stimulating electrodes, acting as controls.
Results: Stimulating iPS–derived cells electrically for prolonged periods (at 1 Hz up to 7 d) *in vitro* increased the maturation of derived cardiomyocytes towards an adult ventricular phenotype as assessed by several measures, including promoting their alignment with the electrical field. *In vivo,* disassociated cells did not survive the transplantation for 4 weeks, but transplanted human cell clumps grew into robust cardiac tissue in the constructs, characterized by troponin T striations interspersed with lectin-stained vessels. The modified bionic chambers described above, which enabled electrical stimulation of developing constructs *in vivo,* thus encouraged the development of contracting constructs in the chamber, incorporating human cardiac cells vascularized profusely by rat host vessels. In preliminary studies to date it was not possible to discern any difference resulting from 3 weeks of electrical stimulation *in vivo*. Further studies with more powerful and prolonged stimulating protocols are underway.
Conclusion: These tissue engineering approaches incorporating endogenous vascularization provide proof-of-principle for generation of substantial, transplantable cardiac tissue from human iPS cells. Electrical stimulation of sufficient power promotes maturation of the cardiomyocytes towards an adult ventricular phenotype, a goal that has eluded many in the field to date.

VITAMIN D SUPPLEMENTATION REDUCES BRAIN INJURY AND INFLAMMATION FOLLOWING ISCHEMIC STROKE

Evans MA[a], Kim HA[a], Ling YH[a], Uong S[a], Drummond GR[ab], Broughton BRS[a], Sobey CG[ab]

[a]Cardiovascular Disease Program, Biomedicine Discovery Institute and Department of Pharmacology Clayton, Victoria, Australia; [b]Department of Surgery, Southern Clinical School, Monash University, Clayton, Victoria, Australia

Background: Following ischemic stroke, inflammation is a major contributor to secondary brain injury and further tissue infarction. Beyond its well-characterized role in calcium metabolism, the active form of vitamin D, 1,25-dihydroxyvitamin D_3 (1,25-VitD3), has been shown to elicit anti-inflammatory actions. Given the contributing role of the immune system in acute post-stroke brain injury, we hypothesized that vitamin D_3 supplementation may reduce brain injury in association with reduced inflammation following stroke.
Aims: To determine whether supplementation of 1,25-VitD3 reduces inflammatory brain injury after ischemic stroke in mice.
Methods: Male C57BL/6 mice (aged 7–10 weeks) were randomly assigned either 1,25-VitD3 (n=32; 100 ng/kg per day i.p.) or vehicle (n=30; mixture of dH_2O, propylene glycol and ethanol) commencing 5 d prior to stroke. Stroke was induced via middle cerebral artery occlusion for 1 h followed by 23 h reperfusion. Twenty-four hours after stroke induction, hanging grip and parallel rod tests were used to assess grip strength and locomotor activity, respectively. In addition, infarct volume was assessed by thionin staining and cerebral inflammation was evaluated using real-time PCR and immunohistochemistry.
Results: Supplementation with 1,25-VitD3 reduced cerebral infarct volume by 50% compared to vehicle (18±3 mm^3 versus 36±6 mm^3, respectively; n=12–14, $P<0.05$). However, at this early time-point there were no differences in functional outcomes, with hanging grip time and total time mobile being similar in 1,25-VitD3- and vehicle-supplemented groups. Expression of key pro-inflammatory cytokines, IL-6, IL-1β and IL-23a, was reduced in brains of mice that received 1,25-VitD3 versus vehicle (n=9–12, $P<0.05$). Expression of the T regulatory cell marker, *FOXP3*, was further elevated in mice supplemented with 1,25-VitD3 (n=11 per group; $P<0.05$). Immunohistochemistry revealed that numbers of neutrophils and T cells infiltrating the ischemic hemisphere were similar in 1,25-VitD3- and vehicle-supplemented groups (n=5–8). Ongoing experiments are assessing other immune cell types, and whether pre-existing vitamin D deficiency predisposes to a worse stroke outcome.
Conclusion: These data indicate that administration of exogenous vitamin D to vitamin D-replete mice can attenuate infarct development and exert anti-inflammatory actions. This may represent a direction for acute stroke therapy.

POST HOC ANALYSIS OF THE EFFECTIVENESS OF BLOOD PRESSURE-LOWERING DRUG TREATMENT BY LEVELS OF ABSOLUTE RISK IN THE ANBP STUDY

Ho CLB[a], Breslin M[a], Doust J[b], Reid CM[c,d], Nelson MR[a]

[a]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; [b]Bond University, Robina, Queensland, Australia; [c]Curtin University,Bentley, Western Australia, Australia; [d]Monash University, Clayton, Victoria, Australia

Background: Cardiovascular disease (CVD) continues to represent a considerable burden on the health care system. International guidelines for the primary prevention of CVD recommend drug treatment for elevated blood pressure (BP) based on BP thresholds with due deference to underlying absolute CVD risk. Guidelines in Australia and New Zealand give pre-eminence to risk stratification using risk calculators to determine BP-lowering drug treatment thresholds. However clinicians are concerned that the average risk approach compared with a BP threshold may be an inferior strategy.
Aims: To examine if BP-lowering treatment based on baseline CVD risk would have superior outcomes compared with a simple BP threshold for those with "mildly" elevated BP.
Methods: We conducted a *post hoc* subgroup analysis of the Australian National Blood Pressure study (ANBP). The ANBP study was a randomized placebo controlled trial, in which participants were recruited from the community with "mildly" elevated diastolic BP between 1973 and 1979. In the present study, we involved participants aged 35 to 69 years. All analyses were based on the "intention to treat." The Cox proportional hazard model was used to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals for participants classified by tertile of Framingham risk scores.
Results: Participants had an average 5-year CVD risk in the intermediate range (10.5±6.5) with moderately elevated BP (159/103 mmHg) and were middle-aged (52±8 years). We identified no significant effect of BP lowering drug treatment on major CVD events with a HR 0.83 (0.65–1.07) or all-cause mortality with a HR 0.75 (0.45–1.36) and a borderline significant effect of stroke with a HR 0.55 (0.31–1.00). In subgroup analyses, the relative and absolute effects did not significantly differ across the CVD risk groups. In terms of absolute benefit, BP-lowering drug treatment significantly reduced the number of events in the high-risk tertile with respect to any event with a number needed to treat (NNT) of 19 (95% CI 11–78), death from any cause with a NNT of 49 (95% CI 26–338)) and major CVD event with a NNT of 23 (95% CI 12–164).
Conclusion: BP-lowering drug treatment produced non-significant effects in the overall study population. Our analysis confirms that the benefit of treatment was substantial only in the high-risk tertile, reaffirming the rationale of treating elevated BP in the setting of all risk factors rather than in isolation.

CCL18 AS A MEDIATOR OF THE PRO-FIBROTIC ACTIONS OF M2 MACROPHAGES IN THE VESSEL WALL DURING HYPERTENSION

Lewis CV[a], Zhu M[a], Lieu M[a], Moodley S[a], Wang Y[a], McConaghy TE[a], Larner B[a], Widdop RE[a], Sobey CG[a], Drummond GR[a], Kemp-Harper BK[a]

[a]Department of Pharmacology, Monash University, Clayton, Victoria, Australia

Background: M2 macrophages contribute to vascular fibrosis and stiffening in hypertension. A potential mediator of these actions is the macrophage-derived, pro-fibrotic chemokine, CCL18, which signals via its cognate receptor, CCR8. Little is known about the role of CCL18 in cardiovascular disease. In addition, the localization and expression of CCR8 in the vascular wall has not been investigated.
Aims: To determine if angiotensin II augments CCL18 production from human primary M2 macrophages, identify cardiovascular targets of CCL18 and investigate the ability of CCL18 to promote fibrosis.

Ho CLB, Breslin M, Chowdhury EK, Doust J, Reid CM, Davis BR, Simpson LM, Nelson MR. Lack of a significant legacy effect of baseline blood pressure' treatment naivety' on all-cause and cardiovascular mortality in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 2020. Journal of hypertension, 38(3), 519-526
doi: 10.1097/HJH.0000000000002280

Protocol

Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review

Chau Le Bao Ho[1], MD; Sharon Sanders[2], BSc, MPH, PhD; Jenny Doust[2], BMBS, FRACGP, PhD; Monique Breslin[1], PhD; Christopher M Reid[3,4], MA, MSc, PhD; Mark Raymond Nelson[1,4], MBBS, MFM, FRACGP, FAFPHM, PhD

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

[2]Centre for Research in Evidence-Based Practice, Bond University, Gold Coast, QLD, Australia

[3]School of Public Health, Curtin University, Perth, WA, Australia

[4]Centre of Cardiovascular Research & Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

Corresponding Author:
Chau Le Bao Ho, MD
Menzies Institute for Medical Research
University of Tasmania
Private Bag 23
Hobart, TAS, 7001
Australia
Phone: 61 406656898
Fax: 61 0362267764
Email: chau.ho@utas.edu.au

Abstract

Background: Many national and international guidelines recommend that the initiation of blood pressure (BP)-lowering drug treatment for the primary prevention of cardiovascular disease (CVD) should no longer be based on BP level alone, but on absolute cardiovascular risk. While BP-lowering drug treatment is beneficial in high-risk individuals at any level of elevated BP, clinicians are concerned about legacy effects on patients with low-to-moderate risk and mildly elevated BP who remain "untreated".

Objective: We aim to investigate the legacy effect of delayed BP-lowering pharmacotherapy in middle-aged individuals (45-65 years) with mildly elevated BP (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) stratified by absolute risk for primary prevention of CVD, but particularly in the low-risk (<10% five-year absolute risk) group.

Methods: Randomized trials of BP-lowering therapy versus placebo or pretreated subjects in active comparator studies with posttrial follow-up will be identified using a 2-step process. First, randomized trials of BP-lowering therapy will be identified by (1) retrieving the references of trials included in published systematic reviews of BP-lowering therapy, (2) retrieving studies published by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), and (3) checking studies referenced in the 1993 World Health Organization/International Society of Hypertension meeting memorandum on BP management. Posttrial follow-up studies will then be identified by forward citation searching the randomized trials identified in step 1 through Web of Science. The search will include randomized controlled trials with at least 1-year in-trial period and a posttrial follow-up phase. Age is the major determinant of absolute cardiovascular risk, so the participants in our review will be restricted to middle-aged adults who are more likely to have a lower cardiovascular risk profile. The primary outcome will be all-cause mortality. Secondary outcomes will include cardiovascular mortality, fatal stroke, fatal myocardial infarction, and death due to heart failure.

Results: The searches for existing systematic reviews and BPLTTC studies were piloted and modified. The study is expected to be completed before June 2018.

Conclusions: The findings of this study will contribute to the body of knowledge concerning the beneficial, neutral, or harmful effects of delayed BP-lowering drug treatment on the primary prevention of CVD in patients with mildly elevated BP and low-to-moderate CVD risk.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews: CRD42017058414; https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058414 (Archived by WebCite® at http://www.webcitation.org/6t6sa8O2Q)

(JMIR Res Protoc 2017;6(9):e177) doi:10.2196/resprot.8362

KEYWORDS

legacy effect; high blood pressure; cardiovascular disease

Introduction

Despite improvements in the management of cardiovascular disease (CVD) over the past five decades, it remains the leading cause of death and disability in the world [1]. CVD was responsible for approximately 17.5 million deaths worldwide in 2012 [1]. In updated guidelines for the primary prevention of CVD from Australasia [2,3], the United Kingdom [4], and Europe [5], blood pressure (BP)-lowering pharmacotherapy is indicated by absolute CVD risk, not BP level alone. In contrast, the US guideline (the Eighth Joint National Committee) [6] is still heavily focused on BP level and age, despite the fact that BP-lowering therapy is beneficial for the reduction of CVD mortality and morbidity at sufficiently high CVD absolute risk, regardless of the level of BP elevation [7]. The use of BP-lowering drug treatment in high-risk settings has achieved consensus in Australasian [2,3], European [5], and the US guidelines [6]. In low-risk individuals, BP-lowering drugs are not recommended by guidelines in Australia [2], New Zealand [3] or the United Kingdom [4], unless BP exceeds a level of 160/100 mmHg, whereas the European [5] and US [6] guidelines recommended an early initiation at a BP level of 140/90 mmHg. However, both approaches raised many concerns from clinicians and a gap still exists between guidelines and clinical practice [8].

An international expert consultation was recently performed to solve the controversy of whether adults with grade 1 hypertension (<140/90 mmHg) and low-to-moderate CVD risk should be treated by drug therapy [9]. Morales-Salinas et al [9] recommended an early initiation of BP-lowering pharmacotherapy primarily from the results of the Heart Outcomes Prevention Evaluation (HOPE-3) trial [10] and a meta-analysis by Thomopoulos et al [11] for adults with grade 1 hypertension and moderate CVD risk; however, the two studies were likely to include a number of high-risk participants. In the HOPE-3 trial [10], participants with an INTERHEART risk score higher than 16 (a value of 16 or higher indicates a high CVD risk) accounted for 32.5% of the total sample [12]. In the meta-analysis by Thomopoulos et al [11], the CVD risk was calculated by CVD death rate in the control group, while the CVD risk score used in most guidelines is for fatal and nonfatal CVD events. Thus, the benefits of BP-lowering pharmacotherapy in low-to-moderate-risk individuals remain unclear, as opposed to the benefits achieved by treating high risk individuals. Most clinicians use BP-lowering pharmacotherapy based on BP criteria alone, due to the perceived potential risk of irreversible target organ damage (the "legacy effect") for delayed therapy [5]. Studies that would help us to answer this question include those that have extended follow-up in the posttrial period. Such studies include the Systolic Hypertension in the Elderly Program trial [13] of approximately 22 years, the Hypertension Detection and Follow-Up Program [14] of 8.3 years, and the second Australian National Blood Pressure study [15] of 10.6 years. Participants in these studies are still likely to be at high baseline risk of CVD due to the advanced age and diabetic status in the inclusion criteria of the trials [13-15]. Hence, the concern of legacy effects on low-to-moderate-risk individuals has not been addressed. Age is the most important determinant of adverse cardiovascular risk, so the participants in our review are restricted to middle-aged adults who are more likely to have a broader cardiovascular risk profile. Therefore, in this systematic review and meta-analysis, we will investigate the effects of BP-lowering drug treatments in middle-aged individuals with mildly elevated BP, stratified by absolute CVD risk.

Methods

Review Objectives

Aim 1

We will conduct a systematic review and meta-analysis of published and unpublished studies of randomized placebo control trials with a posttrial follow-up phase that included middle-aged participants without overt CVD, and examine these studies for CVD mortality and all-cause mortality.

Aim 2

We will conduct a subgroup analysis (where possible) of participants in these trials classified as low-, moderate-, and high-absolute CVD risk by the Framingham Risk Score (FRS) used in the Australia guideline [2], or the risk calculator used by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [16] which uses routine clinical information if information on cholesterol levels is not available for fatal and nonfatal CVD events and all-cause mortality. We will conduct an individual patient data meta-analysis, if data are available.

Primary Null Hypothesis

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at low-absolute CVD risk.

Secondary Hypotheses

Hypothesis 1

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy

initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at moderate-absolute CVD risk.

Hypothesis 2

There will be no significant difference in CVD mortality or all-cause mortality between patients who have drug therapy initiated earlier (active treatment arm) versus delayed or not initiated (control arm) in individuals at high-absolute CVD risk.

Hypothesis 3

In-trial CVD events (fatal and nonfatal) will be incremental by risk classification estimated by FRS or equivalent risk calculated at baseline.

Criteria for Considering Studies in the Review

Population

The study will include men and nonpregnant women from 45 to 65 years of age. At least 80% of participants from each trial must have had mildly elevated BP at baseline, defined as a systolic BP of 140- 159 mmHg and/or diastolic BP 90- 99 mmHg. Furthermore, all included participants must not have exhibited any history of CVD at baseline: myocardial infarction, angina pectoris, coronary bypass surgery, coronary angioplasty, stroke, transient ischaemic attack, carotid endarterectomy, surgery for peripheral vascular disease, intermittent claudication or renal failure (creatinine >1.5 times the upper limit of normal). If trials included participants different than those of interest (eg, secondary prevention, moderately-elevated or highly-elevated BP), we will attempt to access individual patient data and subsequently select participants that meet specific criteria.

Intervention

The study will focus on all types of BP-lowering drugs, except for some types that have limited clinical use due to the risk of side effects and availability (eg, ganglion blockers, reserpine, rauwolfia).

Comparison

The study will compare the effects of BP-lowering drug treatments in active treatment groups versus control treatment groups. However, if comparative trials with two active comparators had an extended posttrial follow-up phase and individual data are available, we will perform a legacy effect analysis per Nelson et al [15]. We will reclassify participants into *previous treatment* (early treatment) groups and *treatment naïve* (delayed treatment) groups. The *previous treatment* group will include participants who were on BP-lowering drug treatments at trial registration and then went on a specific drug withdrawal program. The *treatment naïve* group will include those who were not on any treatments at trial registration.

Outcomes

Primary outcomes will include all-cause mortality in both randomization and follow-up periods. Secondary outcomes will include CVD mortality (defined as deaths due to stroke, myocardial infarction, and heart failure), fatal stroke, fatal myocardial infarction, and fatal heart failure. Nonfatal CVD events will be included if the measurements of outcomes are similar between trials. Vital status in posttrial periods must be assessed by national death databases or equivalent records.

Study Design

Randomized controlled trials with at least 1-year in-trial period and a posttrial follow-up phase.

Language

No restriction (English and non-English studies).

Publication Type

Published and unpublished studies reported in peer-reviewed journals, reports, conference abstracts, and theses.

Search Methods for Identification of Studies

Randomized trials of BP-lowering therapies versus placebo or active comparator with posttrial follow-up periods will be identified using a 2-step process. First, randomized trials of BP-lowering therapy will be identified by (1) retrieving the references of trials included in published systematic reviews of BP-lowering therapy, (2) retrieving studies published by the BPLTTC, and (3) checking studies referenced in the 1993 WHO/ISH (World Health Organization/International Society of Hypertension) meeting memorandum on BP management [17]. To identify existing systematic reviews, we will search Medline Ovid using a combination of Medical Subject Headings and text word terms for BP-lowering regimes and high BP with a systematic review filter (see Multimedia Appendix 1). Web of Science will be used to retrieve the references of studies cited by the systematic reviews, and these will be exported to an Endnote file. To identify studies from the BPLTTC, a text word search in the title, abstract, and author fields will be conducted in Ovid Medline and the retrieved references will be exported to the Endnote file. Web of Science will be used to retrieve the references of studies cited in the WHO/ISH meeting memorandum and these will be exported to the Endnote file. After removing duplications, the Endnote file will be screened to identify randomized trials of BP-lowering therapies versus placebo or active comparators. In the second step of the search, posttrial follow-up studies will be identified by forward citation searching the randomized trials identified in step 1. Web of Science will be used for forward citation searches of each of the original trials, with the citations exported to another Endnote file. After the removal of duplications in the Endnote file, the file will be searched using terms related to extended follow-up (see Multimedia Appendix 2). The resulting titles and abstracts will be screened independently by two reviewers using the review eligibility criteria.

Study Selection

First, two independent reviewers will screen a small sample of papers found in the search to revise any unclear or inappropriate inclusion criteria. In the full selection process, two reviewers will independently scan the results of the search and determine the eligibility of the studies. In the initial screening of titles and abstracts, the studies will be included if they meet the inclusion criteria or they do not have enough information for exclusion. Rejected citations will be recorded and classified as irrelevant studies. All potentially relevant articles will be screened through full text for a final decision. If a paper does not have sufficient

information to assess eligibility, we will attempt to contact the authors; the paper will be classified as a *potentially relevant article* and checked in sensitivity analyses if authors do not reply after one month. If we identify trials that meet our inclusion criteria but lack data on the posttrial follow-up period, we will run a forward citation search from those studies. If a study has multiple citations, we will report separate citations but analyze these reports as a single study. We will also liaise with the BPLTTC for any individual patient data from trials meeting our inclusion criteria.

Data Extraction and Quality Assessment

Data extraction forms (detailed in Textbox 1) and quality assessment forms will be piloted on a small group of studies. Two reviewers will independently perform data extraction and quality assessment in the prespecified form. If any disagreements arise, the reviewers will discuss consensus or consult with the third reviewer. A report of correction or amendments to the prespecified form will be recorded.

Textbox 1. Information required for data extraction.

General information: reviewer performing data extraction, date of data extraction, and identification features of the study (eg, record number, authors, article title, type of publication, country of origin, the source of funding)

Study characteristics: aims of the study, study design, study inclusion and exclusion criteria, recruitment procedures (details of randomization, blinding), and unit of allocation (participant, GP practice)

Participant characteristics: baseline characteristics (age, gender, ethnicity, socioeconomic status, comorbidities, systolic BP, diastolic BP, weight, height, smoking status, serum total cholesterol, serum creatinine level), and the number of participants in active treatment group and control group

Intervention and setting: type and dose of BP-lowering regimen

Outcome data:

- For each outcome: whether reported, definition, length of follow-up, number of events, number of participants in each event, odds ratio, risk ratio, and hazard ratio
- For both intervention groups: number of participants enrolled; number of participants included in analysis; and number of withdrawals, exclusions, and lost to follow-up

Type of analysis used in the study: intention to treat or per protocol

Quality Assessment

The risk of bias will be assessed by two reviewers following the Cochrane Risk of bias tool [18] which includes the following criteria: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel, and outcome (performance and detection bias); and incomplete outcome data (attrition bias). The bias will be assessed as unclear, low-risk, or high-risk. Publication bias will be judged by observing the asymmetry of funnel plots; if they are asymmetric, contour-enhanced funnel plots will then be analyzed to examine whether publication bias alone caused the asymmetry. We will also use Egger's meta-regression model to assess the relationship between the observed effect sizes and the size of studies [19].

Data Synthesis and Analysis

After pooling all eligible studies, we will design a fixed-effect model and assess the heterogeneity by visually inspecting the forest plots, Chi-squared tests, and I^2tests. Statistical heterogeneity will be recorded when the studies' confidence intervals exhibit poor overlap, the P-value of the test of heterogeneity is 0.1 or lower, or the I^2value is 0.5 or greater. In these cases, we will also perform an analysis using a random-effects model. All trial endpoints will be treated as dichotomous variables and grouped by time from randomization. In the fixed-effect model, the Mantel-Haenszel method model will be used to combine risk ratios of each outcome [20]. We will conduct a subgroup analysis in which available risk calculators will be used to stratify participants by the baseline absolute CVD risk for fatal and nonfatal CVD events. In a sensitivity analysis, each study will be removed (one at a time) to assess the impact of each study on the pooled outcomes. The Cochrane software (Revman) [21] will be used for meta-analysis, selective reporting, and other sources of bias.

Ethics and Dissemination

This systematic review will analyze nonidentifiable data; thus, a formal ethics approval is unlikely to be crucial. The study protocol was registered with the International Prospective Register of Systematic Review (PROSPERO) with the reference number CRD42017058414. The current study will contribute a chapter of a PhD thesis (CH).

Results

We are currently in the process of developing the search strategy. The search in Medline via Ovid has been piloted and modified. The analysis is expected to complete before June 2018.

Discussion

Given the strong beliefs held by many clinicians that early treatment of elevated BP is necessary to prevent CVD events, it is not possible to conduct a randomized controlled trial of early versus late treatment at present. This is particularly true for patients with mildly elevated BP and low CVD risk, as studies would require a large sample size of participants or a long follow-up period because approximately 10% of CVD events are expected to occur within 10 years. In addition, clinicians are questioning the real benefits, adverse effects, and

medical costs of the life-long intervention of BP-lowering drug treatment. The findings of this study will contribute to the body of knowledge concerning the beneficial, neutral, or harmful effects of delayed BP-lowering drug treatment in patients with mildly elevated BP and low-to-moderate CVD risk.

Limitations

Due to the changes in definitions of CVD and diagnostic methods used over time, we predict that it will be difficult to combine these outcomes in a meta-analysis. This issue inherently generates bias in selection, detection, attrition, and reporting.

Acknowledgments

CLBH is a PhD candidate at Menzies Institute for Medical Research, and has received a PhD scholarship from Merle Weaver Postgraduate Scholarship. JD is supported by National Health and Medical Research Council Screening and Test Evaluation Program Grant 633003. CR is supported by a National Health and Medical Research Council Senior Research Fellowship (1045862).

Conflicts of Interest

MRN has served on an advisory board for AMGEN in the last 5 years. All other authors declare no conflicts of interest.

Multimedia Appendix 1

Search strategy developed for Medline via Ovid to identify existing systematics review.

[PDF File (Adobe PDF File), 22KB - resprot_v6i9e177_app1.pdf]

Multimedia Appendix 2

Search terms related to extended follow-up.

[PDF File (Adobe PDF File), 19KB - resprot_v6i9e177_app2.pdf]

References

1. World Health Organization. Fact sheet - Cardiovascular disease (CVDs). 2016. URL: http://www.who.int/mediacentre/factsheets/fs317/en/ [accessed 2017-03-22] [WebCite Cache ID 6sYUPV5qR]
2. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012. URL: http://www.cvdcheck.org.au/index.php?option=com_content&view=article&id=47&Itemid=27 [accessed 2017-08-27] [WebCite Cache ID 6t2XC9hGG]
3. New Zealand Guidelines Group. The assessment and management of cardiovascular risk. Wellington, New Zealand; 2003. URL: https://www.health.govt.nz/system/files/documents/publications/cvd_risk_full.pdf [accessed 2017-08-27] [WebCite Cache ID 6t2XIqSLj]
4. National Clinical Guideline Centre UK. Hypertension: the clinical management of primary hypertension in adults: update of clinical guidelines 18 and 34. National Institute for Health and Clinical Excellence: Guidance 2011 Aug. [Medline: 22855971]
5. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press 2014 Feb;23(1):3-16. [doi: 10.3109/08037051.2014.868629] [Medline: 24359485]
6. James P, Oparil S, Carter B, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014 Feb 05;311(5):507-520. [doi: 10.1001/jama.2013.284427] [Medline: 24352797]
7. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009 May 19;338:b1665 [FREE Full text] [Medline: 19454737]
8. Jansen J, Bonner C, McKinn S, Irwig L, Glasziou P, Doust J, et al. General practitioners' use of absolute risk versus individual risk factors in cardiovascular disease prevention: an experimental study. BMJ Open 2014 May 15;4(5):e004812 [FREE Full text] [doi: 10.1136/bmjopen-2014-004812] [Medline: 24833688]
9. Morales SA, Coca A, Olsen M, Sanchez RA, Sebba-Barroso WK, Kones R, et al. Clinical perspective on antihypertensive drug treatment in adults with grade 1 hypertension and low-to-moderate cardiovascular risk: an international expert consultation. Curr Probl Cardiol 2017 Jul;42(7):198-225. [doi: 10.1016/j.cpcardiol.2017.03.001] [Medline: 28552207]
10. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016 May 26;374(21):2009-2020. [doi: 10.1056/NEJMoa1600175] [Medline: 27041480]

11. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. J Hypertens 2014 Dec;32(12):2296-2304. [doi: 10.1097/HJH.0000000000000379] [Medline: 25259547]
12. McGorrian C, Yusuf S, Islam S, Jung H, Rangarajan S, Avezum A, INTERHEART Investigators. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score. Eur Heart J 2011 Mar;32(5):581-589. [doi: 10.1093/eurheartj/ehq448] [Medline: 21177699]
13. Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 2011 Dec 21;306(23):2588-2593. [doi: 10.1001/jama.2011.1821] [Medline: 22187278]
14. Hypertension Detection and Follow-up Program Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. JAMA 1988 Apr 08;259(14):2113-2122. [Medline: 3346988]
15. Nelson M, Chowdhury E, Doust J, Reid C, Wing L. Ten-year legacy effects of baseline blood pressure 'treatment naivety' in the Second Australian National Blood Pressure study. J Hypertens 2015 Nov;33(11):2331-2337. [doi: 10.1097/HJH.0000000000000709] [Medline: 26335432]
16. Blood Pressure Lowering Treatment Trialists' Collaboration, Sundström J, Arima H, Woodward M, Jackson R, Karmali K, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014 Aug 16;384(9943):591-598. [doi: 10.1016/S0140-6736(14)61212-5] [Medline: 25131978]
17. Zanchetti A, Chalmers JP, Arakawa K, Gyarfas I, Hamet P, Hansson L, et al. The 1993 guidelines for the management of mild hypertension: memorandum from a WHO/ISH meeting. Blood Press 1993 Jun;2(2):86-100. [Medline: 8180730]
18. Higgins J, Altman D, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928 [FREE Full text] [Medline: 22008217]
19. Chaimani A, Mavridis D, Salanti G. A hands-on practical tutorial on performing meta-analysis with Stata. Evid Based Ment Health 2014 Nov;17(4):111-116. [doi: 10.1136/eb-2014-101967] [Medline: 25288685]
20. Mantel N, Haenzel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959 Apr;22(4):719-748. [Medline: 13655060]
21. The Cochrane Collaboration. Review Manager (RevMan). Copenhagen: The Nordic Cochrane Centre; 2014. [Computer program]. Version 5.3 URL: http://community.cochrane.org/tools/review-production-tools/revman-5/about-revman-5 [accessed 2017-08-29] [WebCite Cache ID 6t4EBl0ok]

Abbreviations

BP: blood pressure
BPLTTC: Blood Pressure Lowering Treatment Trialists' Collaboration
CVD: cardiovascular disease
FRS: Framingham Risk Score
HOPE-3: Heart Outcomes Prevention Evaluation trial
WHO/ISH: World Health Organization/International Society of Hypertension

Edited by G Eysenbach; submitted 06.07.17; peer-reviewed by P Sever; comments to author 15.07.17; revised version received 20.07.17; accepted 21.07.17; published 01.09.17

Please cite as:
Ho CLB, Sanders S, Doust J, Breslin M, Reid CM, Nelson MR
Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review
JMIR Res Protoc 2017;6(9):e177
URL: http://www.researchprotocols.org/2017/9/e177/
doi:10.2196/resprot.8362
PMID:28864428

Ho, C. L. B., Chowdhury, E. K., Breslin, M., Doust, J., Reid, C. M., Wing, L. M., Nelson, M. R., 2019. Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study, Journal of clinical lipidology, 13(1), 148-155

References

1. Ministry of Health. Cardiovascular Disease Risk Assessment and Management for Primary Care. Wellington: Ministry of Health; 2018.

2. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012.

3. Nerenberg Kara A., Zarnke Kelly B., Leung Alexander A., Dasgupta Kaberi, Butalia Sonia, McBrien Kerry, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol 2018;34(5):506-25.

4. Whelton Paul K., Carey Robert M., Aronow Wilbert S., Casey Donald E., Collins Karen J., Dennison Himmelfarb Cheryl, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71(6):e13-e115.

5. NICE clinical guideline. Hypertension clinical management of primary hypertension adults. guidance.nice.org.uk/cg127. 2011.

6. GBD 2015 Mortality and Causes of Death Collaborators and others. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 2016;388(10053):1459-544.

7. Roth Gregory A, Johnson Catherine, Abajobir Amanuel, Abd-Allah Foad, Abera Semaw Ferede, Abyu Gebre, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70(1):1-25.

8. World Health Organization. Cardiovascular Disease: Global Atlas on Cardiovascular Disease Prevention and Control. Geneva, Switzerland: WHO; 2012.

9. Murray Christopher J. L., Vos Theo, Lozano Rafael, Naghavi Mohsen, Flaxman Abraham D., Michaud Catherine, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet;380(9859):2197-223.

10. Yusuf Salim, Reddy Srinath, Ôunpuu Stephanie, Anand Sonia. Global Burden of Cardiovascular Diseases. Part I: General Considerations, the Epidemiologic Transition, Risk Factors, and Impact of Urbanization 2001;104(22):2746-53.

11. Cohen Barney. Urban Growth in Developing Countries: A Review of Current Trends and a Caution Regarding Existing Forecasts. World Development 2004;32(1):23-51.

12. Popkin Barry M. The Nutrition Transition and Obesity in the Developing World. The Journal of Nutrition 2001;131(3):871S-3S.

13. Critchley Julia, Liu Jing, Zhao Dong, Wei Wang, Capewell Simon. Explaining the Increase in Coronary Heart Disease Mortality in Beijing Between 1984 and 1999. Circulation 2004;110(10):1236-44.

14. Roth Gregory A., Huffman Mark D., Moran Andrew E., Feigin Valery, Mensah George A., Naghavi Mohsen, et al. Global and Regional Patterns in Cardiovascular Mortality From 1990 to 2013. Circulation 2015;132(17):1667-78.

15. Yusuf Salim, Rangarajan Sumathy, Teo Koon, Islam Shofiqul, Li Wei, Liu Lisheng, et al. Cardiovascular Risk and Events in 17 Low-, Middle-, and High-Income Countries. New England Journal of Medicine 2014;371(9):818-27.

16. World Health Organization and World Economic Forum. From Burden to “Best Buys”: Reducing the Economic Impact of NCDs in Lowand Middle-Income Countries. Geneva, Switzerland: WHO; 2011.

17. Rosamond Wayne D., Chambless Lloyd E., Folsom Aaron R., Cooper Lawton S., Conwill David E., Clegg Limin, et al. Trends in the Incidence of Myocardial Infarction and in Mortality Due to Coronary Heart Disease, 1987 to 1994. New England Journal of Medicine 1998;339(13):861-7.

18. Beaglehole Robert. International trends in coronary heart disease mortality and incidence rates. Journal of cardiovascular risk 1999;6(2):63-8.

19. Mirzaei M, Truswell A S, Taylor R, Leeder S R. Coronary heart disease epidemics: not all the same. Heart 2009;95(9):740-6.

20. Lee Sally, Shafe Anna C E, Cowie Martin R. UK stroke incidence, mortality and cardiovascular risk management 1999–2008: time-trend analysis from the General Practice Research Database. BMJ Open 2011;1(2).

21. Feigin Valery L., Lawes Carlene M. M., Bennett Derrick A., Barker-Collo Suzanne L., Parag Varsha. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. The Lancet Neurology;8(4):355-69.

22. Rose G. Strategy of prevention: lessons from cardiovascular disease. British Medical Journal (Clinical research ed.) 1981;282(6279):1847-51.

23. Hunink M. M., Goldman L., Tosteson A. A., et al. The recent decline in mortality from coronary heart disease, 1980-1990: The effect of secular trends in risk factors and treatment. JAMA 1997;277(7):535-42.

24. Capewell S, Morrison C E, McMurray J J. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart 1999;81(4):380-6.

25. Capewell Simon, Beaglehole Robert, Seddon Mary, McMurray John. Explanation for the Decline in Coronary Heart Disease Mortality Rates in Auckland, New Zealand, Between 1982 and 1993. Circulation 2000;102(13):1511-6.

26. Jadelson P. Andrade Fausto J. Pinto, Donna K. Arnett. Prevention of Cardiovascular Diseases: From current evidence to clinical practice: Springer International Publishing AG Switzerland; 2014.

27. Davies Alisha Ruth, Smeeth Liam, Grundy Emily Marjatta Dorothea. Contribution of changes in incidence and mortality to trends in the prevalence of coronary heart disease in the UK: 1996–2005. European Heart Journal 2007;28(17):2142-7.

28. Fuster Valentin, Mearns Bryony M. The CVD paradox: mortality vs prevalence. Nat Rev Cardiol 2009;6(11):669-.

29. Association American Heart. Cardiovascular disease: A costly burden for America projections through 2035. Washington DC: American Heart Association 2017.

30. Murray Christopher JL, Lopez Alan D, Organization World Health. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary. 1996.

31. Abegunde Dele O., Mathers Colin D., Adam Taghreed, Ortegon Monica, Strong Kathleen. The burden and costs of chronic diseases in low-income and middle-income countries. The Lancet;370(9603):1929-38.

32. Capewell Simon, Allender Steven, Critchley Julia, Lloyd-Williams Ffion, O'Flaherty Martin, Rayner Mike, et al. Modelling the UK burden of cardiovascular disease to 2020. London: Cardiovascular Coalition 2008.

33. Mathers Colin D., Loncar Dejan. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLoS Medicine 2006;3(11):e442.

34. Wong Nathan D. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014;11(5):276-89.

35. World Health Organisation. The challenge of cardiovascular disease – quick statistics; 2016 29 May 2018]; Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics.

36. Barton Pelham, Andronis Lazaros, Briggs Andrew, McPherson Klim, Capewell Simon. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. BMJ 2011;343.

37. Muntner Paul, Whelton Paul K. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. Journal of the American College of Cardiology 2017;69(19):2446-56.

38. Williams Bryan. Recent hypertension trials: implications and controversies. Journal of the American College of Cardiology 2005;45(6):813-27.

39. National Cholesterol Education Program Adult Treatment Panel III. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.

40. Piepoli Massimo F., Hoes Arno W., Agewall Stefan, Albus Christian, Brotons Carlos, Catapano Alberico L., et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practiceThe Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal 2016;37(29):2315-81.

41. James Paul A, Oparil Suzanne, Carter Barry L, Cushman William C, Dennison-Himmelfarb Cheryl, Handler Joel, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama 2014;311(5):507-20.

42. D'Agostino Ralph B., Vasan Ramachandran S., Pencina Michael J., Wolf Philip A., Cobain Mark, Massaro Joseph M., et al. General Cardiovascular Risk Profile for Use in Primary Care. The Framingham Heart Study 2008;117(6):743-53.

43. Anderson KM, Odell PM, Wilson PW, WB.K. Cardiovascular disease risk profiles. American Heart Journal 1991;121:293-8.

44. Anderson Keaven M, Wilson PW, Odell Patricia M, Kannel William B. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83(1):356-62.

45. Conroy RM, Pyörälä K, Fitzgerald AP el, Sans S, Menotti A, De Backer Gui, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European heart journal 2003;24(11):987-1003.

46. Hippisley-Cox Julia, Coupland Carol, Vinogradova Yana, Robson John, Minhas Rubin, Sheikh Aziz, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008;336(7659):1475-82.

47. Pylypchuk Romana, Wells Sue, Kerr Andrew, Poppe Katrina, Riddell Tania, Harwood Matire, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. The Lancet 2018;391(10133):1897-907.

48. Lloyd-Jones Donald M, Wilson Peter WF, Larson Martin G, Beiser Alexa, Leip Eric P, D'Agostino Ralph B, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. American Journal of Cardiology 2004;94(1):20-4.

49. Joint British Societies Boards. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;100(Suppl 2):ii1-ii67.

50. Bonner Carissa, Bell Katy, Jansen Jesse, Glasziou Paul, Irwig Les, Doust Jenny, et al. Should heart age calculators be used alongside absolute cardiovascular disease risk assessment? BMC cardiovascular disorders 2018;18(1):19.

51. Wang Jianjun, Ruotsalainen Sanna, Moilanen Leena, Lepistö Päivi, Laakso Markku, Kuusisto Johanna. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. European heart journal 2007;28(7):857-64.

52. Thomas Frédérique, Pannier Bruno, Benetos Athanase, Vischer Ulrich M. The impact of the metabolic syndrome–but not of hypertension–on all-cause mortality disappears in the elderly. Journal of hypertension 2011;29(4):663-8.

53. Vischer Ulrich Max, Safar ME, Safar H, Iaria P, Le Dudal K, Henry O, et al. Cardiometabolic determinants of mortality in a geriatric population: is there a “reverse metabolic syndrome”? Diabetes & Metabolism 2009;35(2):108-14.

54. van Hateren Kornelis JJ, Landman Gijs WD, Kleefstra Nanne, Groenier Klaas H, Kamper Adriaan M, Houweling Sebastiaan T, et al. Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12). Age and ageing 2010;39(5):603-9.

55. Boshuizen Hendriek C, Izaks Gerbrand J, van Buuren Stef, Ligthart Gerard J. Blood pressure and mortality in elderly people aged 85 and older: community based study. Bmj 1998;316(7147):1780-4.

56. Rapsomaniki Eleni, Timmis Adam, George Julie, Pujades-Rodriguez Mar, Shah Anoop D, Denaxas Spiros, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1· 25 million people. The Lancet 2014;383(9932):1899-911.

57. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence: Guidance. In: Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London: National Institute for Health and Care Excellence (UK). Copyright (c) National Clinical Guideline Centre, 2014.; 2014.

58. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults Melbourne: National Heart Foundation of Australia; 2016.

59. Williams Bryan, Mancia Giuseppe, Spiering Wilko, Agabiti Rosei Enrico, Azizi Michel, Burnier Michel, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018.

60. Anderson Todd J, Grégoire Jean, Pearson Glen J, Barry Arden R, Couture Patrick, Dawes Martin, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32(11):1263-82.

61. Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease. Edinburgh: SIGN; 2017.

62. Woodward Mark, Brindle Peter, Tunstall-Pedoe Hugh. Adding social deprivation and family history to cardiovascular risk assessment-the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2006.

63. Whelton Paul K., Carey Robert M., Aronow Wilbert S., Casey Donald E., Collins Karen J., Dennison Himmelfarb Cheryl, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines 2017.

64. Goff David C., Lloyd-Jones Donald M., Bennett Glen, Coady Sean, D'Agostino Ralph B., Gibbons Raymond, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25, Part B):2935-59.

65. Grundy Scott M., Stone Neil J., Bailey Alison L., Beam Craig, Birtcher Kim K., Blumenthal Roger S., et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines 2018:25709.

66. Bibbins-Domingo Kirsten, Grossman David C, Curry Susan J, Davidson Karina W, Epling John W, García Francisco AR, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. Jama 2016;316(19):1997-2007.

67. Gueyffier Francois, Boutitie Florent, Boissel Jean-Pierre, Pocock Stuart, Coope John, Cutler Jeffrey, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: a meta-analysis of individual patient data from randomized, controlled trials. Ann Intern Med 1997;126(10):761-7.

68. Collaboration Blood Pressure Lowering Treatment Trialists'. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. The Lancet 2000;356(9246):1955-64.

69. Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. J Cardiovasc Pharmacol 1996;27:S49-54.

70. Law M R, Morris J K, Wald N J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338.

71. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. Bmj 2003;326(7404):1427.

72. Fretheim Atle, Odgaard-Jensen Jan, Brørs Odd, Madsen Steinar, Njølstad Inger, Norheim Ole F., et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med 2012;10(1):33.

73. Collaboration Blood Pressure Lowering Treatment Trialists'. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. The Lancet 2003;362(9395):1527-35.

74. Ettehad Dena, Emdin Connor A, Kiran Amit, Anderson Simon G, Callender Thomas, Emberson Jonathan, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet 2016;387(10022):957-67.

75. Domenic Sica. Are There Pleiotropic Effects of Antihypertensive Medications or Is It All About the Blood Pressure in the Patient With Diabetes and Hypertension? The Journal of Clinical Hypertension 2011;13(4):301-4.

76. Chow Clara K., Thakkar Jay, Bennett Alex, Hillis Graham, Burke Michael, Usherwood Tim, et al. Quarter-dose quadruple combination therapy

for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. The Lancet 2017;389(10073):1035-42.

77. Pfeffer Marc A., McMurray John J.V. Lessons in Uncertainty and Humility — Clinical Trials Involving Hypertension. New England Journal of Medicine 2016;375(18):1756-66.

78. Neaton J. D., Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease overall findings and differences by age for 316099 white men. Archives of Internal Medicine 1992;152(1):56-64.

79. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. The Lancet 2002;360(9349):1903-13.

80. Trialists'Collaboration Blood Pressure Lowering Treatment. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger people: meta-analysis of randomised trials. Bmj 2008;336:1121-3.

81. Turnbull Fiona, Woodward Mark, Neal Bruce, Barzi Federica, Ninomiya Toshiharu, Chalmers John, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. European heart journal 2008;29(21):2669-80.

82. Trialists'Collaboration Blood Pressure Lowering Treatment. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005;165(12):1410-9.

83. Blood Pressure Lowering Treatment Trialists'Collaboration. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. Bmj 2013;347:f5680.

84. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. The Lancet 2014;384(9943):591-8.

85. Thomopoulos Costas, Parati Gianfranco, Zanchetti Alberto. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk–overview and meta-analyses of randomized trials. Journal of hypertension 2014;32(12):2305-14.

86. Karmali Kunal N, Lloyd-Jones Donald M. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. Hypertension 2017;69(3):e2-e9.

87. Sussman Jeremy, Vijan Sandeep, Hayward Rod. Using benefit-based tailored treatment to improve the use of antihypertensive medications. Circulation 2013:CIRCULATIONAHA. 113.002290.

88. Sundström Johan, Arima Hisatomi, Jackson Rod, Turnbull Fiona, Rahimi Kazem, Chalmers John, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Annals of internal medicine 2015;162(3):184-91.

89. Thomopoulos Costas, Parati Gianfranco, Zanchetti Alberto. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. Journal of hypertension 2014;32(12):2296-304.

90. Xie Xinfang, Atkins Emily, Lv Jicheng, Bennett Alexander, Neal Bruce, Ninomiya Toshiharu, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. The Lancet 2016;387(10017):435-43.

91. Czernichow Sébastien, Zanchetti Alberto, Turnbull Fiona, Barzi Federica, Ninomiya Toshiaru, Kengne André-Pascal, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. Journal of hypertension 2011;29(1):4-16.

92. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. New England Journal of Medicine 2015;373(22):2103-16.

93. Thomopoulos Costas, Parati Gianfranco, Zanchetti Alberto. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. Journal of Hypertension 2017;35(11):2150-60.

94. Bangalore Sripal, Toklu Bora, Gianos Eugenia, Schwartzbard Arthur, Weintraub Howard, Ogedegbe Gbenga, et al. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. The American journal of medicine 2017;130(6):707-19. e8.

95. Verdecchia Paolo, Angeli Fabio, Gentile Giorgio, Reboldi Gianpaolo. More versus less intensive blood pressure–lowering strategy: cumulative evidence and trial sequential analysis. Hypertension 2016:HYPERTENSIONAHA. 116.07608.

96. Thomopoulos Costas, Parati Gianfranco, Zanchetti Alberto. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension. 11. Effects of total cardiovascular risk and achieved blood pressure: overview and meta-analyses of randomized trials. Journal of hypertension 2017;35(11):2138-49.

97. Lonn Eva M, Bosch Jackie, López-Jaramillo Patricio, Zhu Jun, Liu Lisheng, Pais Prem, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. New England Journal of Medicine 2016;374(21):2009-20.

98. Dagenais Gilles R, Jung Hyejung, Lonn Eva, Bogaty Peter M, Dehghan Mahshid, Held Claes, et al. Effects of Lipid-Lowering and Antihypertensive Treatments in Addition to Healthy Lifestyles in Primary Prevention: An Analysis of the HOPE-3 Trial. Journal of the American Heart Association 2018;7(15):e008918.

99. Emdin Connor A, Rahimi Kazem, Neal Bruce, Callender Thomas, Perkovic Vlado, Patel Anushka. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. Jama 2015;313(6):603-15.

100. Heerspink Hiddo J Lambers, Ninomiya Toshiharu, Zoungas Sophia, de Zeeuw Dick, Grobbee Diederick E, Jardine Meg J, et al. Effect of lowering blood

pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. The Lancet 2009;373(9668):1009-15.

101. Thomopoulos Costas, Parati Gianfranco, Zanchetti Alberto. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. Journal of hypertension 2014;32(12):2285-95.

102. van Dieren Susan, Kengne Andre P, Chalmers John, Beulens Joline WJ, Cooper Mark E, Grobbee Diederick E, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. Diabetes Res Clin Pract 2012;98(1):83-90.

103. Montgomery Alan A, Fahey Tom, Ben-Shlomo Yoav, Harding James. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. Journal of hypertension 2003;21(9):1753-9.

104. Kassaï Behrouz, Boissel Jean-Pierre, Cucherat Michel, Boutitie Florent, Gueyffier François. Treatment of high blood pressure and gain in event-free life expectancy. Vascular health and risk management 2005;1(2):163.

105. Diao D , Wright JM , Cundiff DK , Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database of Systematic Reviews 2012;8:CD006742.

106. Sheppard James P., Stevens Sarah, Stevens Richard, Martin Una, Mant Jonathan, Hobbs F. D. Richard, et al. Benefits and Harms of Antihypertensive Treatment in Low-Risk Patients With Mild Hypertension. JAMA Internal Medicine 2018;178(12):1626-34.

107. Brunström Mattias, Carlberg Bo. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Internal Medicine 2018;178(1):28-36.

108. Wilkins J. T., Ning H., Berry J., Zhao L., Dyer A. R., Lloyd-Jones D. M. LIfetime risk and years lived free of total cardiovascular disease. JAMA 2012;308(17):1795-801.

109. Zanchetti Alberto. Residual Risk in Treated Hypertension. In: Special Issues in Hypertension: Springer; 2012. p. 309-21.

110. Zanchetti Alberto. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? Journal of hypertension 2009;27(8):1509-20.

111. Blacher J, Evans A, Arveiler D, Amouyel P, Ferrieres J, Bingham A, et al. Residual cardiovascular risk in treated hypertension and hyperlipidaemia: the PRIME Study. Journal of human hypertension 2010;24(1):19.

112. Simpson Scot H, Eurich Dean T, Majumdar Sumit R, Padwal Rajdeep S, Tsuyuki Ross T, Varney Janice, et al. A meta-analysis of the association between adherence to drug therapy and mortality. Bmj 2006;333(7557):15.

113. Rothwell Peter M, Howard Sally C, Dolan Eamon, O'Brien Eoin, Dobson Joanna E, Dahlöf Bjorn, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. The Lancet 2010;375(9718):895-905.

114. Leren P., Helgeland A. Oslo Hypertension Study. Drugs 1986;31 Suppl 1:41-5.

115. Holme I, Kjeldsen Se. Long-term survival in the randomized trial of drug treatment in mild to moderate hypertension of the Oslo study 1972-3. Eur J Intern Med [serial online] 2015;26(2):123-6. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/814/CN-01051814/frame.html

https://ac-els-cdn-com.ezproxy.utas.edu.au/S0953620515000321/1-s2.0-S0953620515000321-main.pdf?_tid=bb06ea32-cd15-11e7-8a97-00000aacb362&acdnat=1511088068_479981dc9deb895a21d5181b3e5dac72.

116. Leren Paul, Helgeland Anders. Coronary heart disease and treatment of hypertension some Oslo study data. The American journal of medicine 1986;80(2):3-6.

117. Asselbergs Folkert W, Diercks Gilles FH, Hillege Hans L, van Boven Ad J, Janssen Wilbert MT, Voors Adriaan A, et al. Effects of fosinopril and

pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110(18):2809-16.

118. Brouwers Fp, Asselbergs Fw, Hillege Hl, Boer Ra, Gansevoort Rt, Veldhuisen Dj, et al. Long-term effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria: ten years of follow-up of Prevention of Renal and Vascular End-stage Disease Intervention Trial (PREVEND IT). American heart journal [serial online] 2011;161(6):1171-8. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/535/CN-00799535/frame.html

https://ac-els-cdn-com.ezproxy.utas.edu.au/S0002870311002584/1-s2.0-S0002870311002584-main.pdf?_tid=1069358a-cd15-11e7-8c97-00000aacb360&acdnat=1511087781_3068cf89069d36c5e30b8ec9ac1be55a.

119. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). Jama 1991;265(24):3255-64.

120. Patel Alpesh B, Kostis John B, Wilson Alan C, Shea Michael L, Pressel Sara L, Davis Barry R. Long-term fatal outcomes in subjects with stroke or transient ischemic attack: fourteen-year follow-up of the systolic hypertension in the elderly program. Stroke 2008;39(4):1084-9.

121. Kostis J. B., Cabrera J., Cheng J. Q., et al. ASsociation between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 2011;306(23):2588-93.

122. Staessen J. A., Thijsq L., Fagard R, Celis H, Birkenhager WH, Bulpitt CJ, et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J hypertens 2004;22(4):847-57.

123. Staessen Jan A, Fagard Robert, Thijs Lutgarde, Celis Hilde, Arabidze Guramy G, Birkenhäger Willem H, et al. Randomised double-blind comparison

of placebo and active treatment for older patients with isolated systolic hypertension. The Lancet 1997;350(9080):757-64.

124. Roberts William C. The Friedewald-Levy-Fredrickson formula for calculating low-density lipoprotein cholesterol, the basis for lipid-lowering therapy. 1988.

125. Investigators Aim-High. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. New England Journal of Medicine 2011;365(24):2255-67.

126. Group HPS2-Thrive Collaborative. Effects of extended-release niacin with laropiprant in high-risk patients. New England Journal of Medicine 2014;371(3):203-12.

127. Taylor Fiona, Ward Kirsten, Moore Theresa HM, Burke Margaret, Smith George Davey, Casas Juan P, et al. Statins for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews 2011(1):CD004816.

128. Law Malcolm R, Wald Nicholas J, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. Bmj 2003;326(7404):1423.

129. Etemad Lida. Statins and potentially interacting medications: a managed care perspective. Preventive medicine in managed care—statin drug interactions and implications for managed care. Am J Manag Care 2004;4(suppl 2):S27-S9.

130. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Elsevier; 2010.

131. Mills EJ, Wu P, Chong G, Ghement I, Singh Sonal, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. QJM: An International Journal of Medicine 2010;104(2):109-24.

132. Chou Roger, Dana Tracy, Blazina Ian, Daeges Monica, Jeanne Thomas L. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. Jama 2016;316(19):2008-24.

133. Taylor Fiona, Huffman Mark D., Macedo Ana Filipa, Moore Theresa H. M., Burke Margaret, Davey Smith George, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013(1).

134. Collins Rory, Reith Christina, Emberson Jonathan, Armitage Jane, Baigent Colin, Blackwell Lisa, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. The Lancet 2016;388(10059):2532-61.

135. Stone Neil J., Robinson Jennifer, Lichtenstein Alice H., Merz C. Noel Bairey, Blum Conrad B., Eckel Robert H., et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2013.

136. Frick M Heikki, Elo Olli, Haapa Kauko, Heinonen Olli P, Heinsalmi Pertti, Helo Pekka, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. New England Journal of Medicine 1987;317(20):1237-45.

137. Jun Min, Foote Celine, Lv Jicheng, Neal Bruce, Patel Anushka, Nicholls Stephen J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. The Lancet 2010;375(9729):1875-84.

138. Zhou Yu-Hao, Ye Xiao-Fei, Yu Fei-Fei, Zhang Xiao, Qin Ying-Yi, Lu Jian, et al. Lipid management in the prevention of stroke: a meta-analysis of fibrates for stroke prevention. BMC Neurol 2013;13(1):1.

139. Saha Sandeep Ajoy, Kizhakepunnur Lenney G, Bahekar Amol, Arora Rohit R. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. American heart journal 2007;154(5):943-53.

140. The lipid research clinics coronary primary prevention trial results: I. reduction in incidence of coronary heart disease. JAMA 1984;251(3):351-64.

141. Dujovne Carlos A, Ettinger Mark P, McNeer J Frederick, Lipka Leslie J, LeBeaut Alexandre P, Suresh Ramachandran, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. The American journal of cardiology 2002;90(10):1092-7.

142. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. European heart journal 2003;24(8):729-41.

143. Baigent Colin, Landray Martin J, Reith Christina, Emberson Jonathan, Wheeler David C, Tomson Charles, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. The Lancet 2011;377(9784):2181-92.

144. Schandelmaier Stefan, Briel Matthias, Saccilotto Ramon, Olu Kelechi K, Arpagaus Armon, Hemkens Lars G, et al. Niacin for primary and secondary prevention of cardiovascular events. The Cochrane database of systematic reviews 2017;6:CD009744-CD.

145. Ip Chi-kin, Jin Dong-mei, Gao Jia-jia, Meng Zhe, Meng Jing, Tan Zhi, et al. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: a meta-analysis of randomized controlled trials. International journal of cardiology 2015;191:138-48.

146. Navarese Eliano Pio, Kołodziejczak Michalina, Schulze Volker, Gurbel Paul A, Tantry Udaya, Lin Yingfeng, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med 2015;163(1):40-51.

147. Lipinski Michael J, Benedetto Umberto, Escarcega Ricardo O, Biondi-Zoccai Giuseppe, Lhermusier Thibault, Baker Nevin C, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid

levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. European heart journal 2015;37(6):536-45.

148. Jakob Tobias, Nordmann Alain J, Schandelmaier Stefan, Ferreira-González Ignacio, Briel Matthias. Fibrates for primary prevention of cardiovascular disease events. The Cochrane Library 2016.

149. Rifkind BM. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. J Am Med Assoc 1984;251:351-64.

150. Hammersley Daniel, Signy Mark. Ezetimibe: an update on its clinical usefulness in specific patient groups. Therapeutic advances in chronic disease 2017;8(1):4-11.

151. Shepherd James, Blauw Gerard J., Murphy Michael B., Bollen Edward L. E. M., Buckley Brendan M., Cobbe Stuart M., et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. The Lancet 2002;360(9346):1623-30.

152. Ridker Paul M, Pradhan Aruna, MacFadyen Jean G, Libby Peter, Glynn Robert J. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. The Lancet 2012;380(9841):565-71.

153. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RGJ, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. Bmj 2009;338:b2376.

154. Savarese Gianluigi, Gotto Antonio M., Paolillo Stefania, D'Amore Carmen, Losco Teresa, Musella Francesca, et al. Benefits of Statins in Elderly Subjects Without Established Cardiovascular Disease: A Meta-Analysis. J Am Coll Cardiol 2013;62(22):2090-9.

155. Sever Peter S, Dahlöf Björn, Poulter Neil R, Wedel Hans, Beevers Gareth, Caulfield Mark, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes

Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. The Lancet 2003;361(9364):1149-58.

156. Colhoun Helen M, Betteridge D John, Durrington Paul N, Hitman Graham A, Neil H Andrew W, Livingstone Shona J, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. The Lancet 2004;364(9435):685-96.

157. Ridker Paul M, Lonn Eva, Paynter Nina P, Glynn Robert, Yusuf Salim. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. Circulation 2017;135(20):1979-81.

158. ALLHAT Officers. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipi. Jama 2002;288:2981-97.

159. Margolis Karen L, Davis Barry R, Baimbridge Charles, Ciocon Jerry O, Cuyjet Aloysius B, Dart Richard A, et al. Long-Term Follow-Up of Moderately Hypercholesterolemic Hypertensive Patients Following Randomization to Pravastatin vs Usual Care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). The Journal of Clinical Hypertension 2013;15(8):542-54.

160. Lloyd Suzanne M, Stott David J, de Craen Anton JM, Kearney Patricia M, Sattar Naveed, Perry Ivan, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PLoS One 2013;8(9):e72642.

161. World Health Organisation. The top 10 causes of death [online database] [cited 2015 13 November]; Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

162. Australian Bureau of Statistics. Causes of Death, Australia, cat. no 3303.3; 2013 [cited 2015 17 July]; Available from:

http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/3303.0~2013~Main%20Features~Leading%20Causes%20of%20Death~10001.

163. Australian Bureau of Statistics. 2012. Causes of death, Australia, 2012. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features10001201 (accessed 13 Nov 2015), [cited Access Date]; Available from: URL.

164. World Health Organisation (WHO). A Global Brief on Hypertension: Silent Killer, Global Public Health Crissis [Online]; 2013 [cited 2015 13th November].

165. TheTask Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens 2013;31:1281-357.

166. Krause Taryn, Lovibond Kate, Caulfield Mark, McCormack Terry, Williams Bryan. Management of hypertension: summary of NICE guidance. Bmj 2011;343:d4891.

167. Organization World Health, Group International Society of Hypertension Writing. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. Journal of hypertension 2003;21(11):1983-92.

168. Weber Michael A, Schiffrin Ernesto L, White William B, Mann Samuel, Lindholm Lars H, Kenerson John G, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. The journal of clinical hypertension 2014;16(1):14-26.

169. Chobanian Aram V, Bakris George L, Black Henry R, Cushman William C, Green Lee A, Izzo Joseph L, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42(6):1206-52.

170. Mitka Mike. Groups spar over new hypertension guidelines. JAMA 2014;311(7):663-4.

171. Guallar Eliseo, Laine Christine. Controversy over clinical guidelines: listen to the evidence, not the noise. Ann Intern Med 2014;160(5):361-2.

172. Wright Jackson T, Fine Lawrence J, Lackland Daniel T, Ogedegbe Gbenga, Himmelfarb Cheryl R Dennison. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med 2014;160(7):499-503.

173. Salinas Alberto Morales, Coca Antonio, Olsen Michael H, Sanchez Ramiro A, Sebba-Barroso Weimar K, Kones Richard, et al. Clinical perspective on antihypertensive drug treatment in adults with grade 1 hypertension and low-to-moderate cardiovascular risk: an international expert consultation. Curr Probl Cardiol 2017;42(7):198-225.

174. The Management Committee. The Australian Therapeutic Trial in Mild Hypertension. The Lancet 1980;315(8181):1261-7.

175. Mancia Giuseppe, Fagard Robert, Narkiewicz Krzysztof, Redon Josep, Zanchetti Alberto, Böhm Michael, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Pressure 2013;22(4):193-278.

176. Bennett Stan A, Magnus Paul. Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980-1989. The Medical Journal of Australia 1994;161(9):519-27.

177. Hajifathalian Kaveh, Ueda Peter, Lu Yuan, Woodward Mark, Ahmadvand Alireza, Aguilar-Salinas Carlos A, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. The Lancet Diabetes & Endocrinology 2015;3(5):339-55.

178. Bender Ralf, Kromp Mandy, Kiefer Corinna, Sturtz Sibylle. Absolute risks rather than incidence rates should be used to estimate the number needed to treat from time-to-event data. Journal of clinical epidemiology 2013;66(9):1038-44.

179. Brookes Sara T, Whitely Elise, Egger Matthias, Smith George Davey, Mulheran Paul A, Peters Tim J. Subgroup analyses in randomized trials: risks

of subgroup-specific analyses;: power and sample size for the interaction test. J Clin Epidemiol 2004;57(3):229-36.

180. Zomer Ella, Owen Alice, Magliano Dianna J, Liew Danny, Reid Chris. Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the 'old'versus the 'new'Framingham equation. Eur J Cardiovasc Prev Rehabil 2011;18(1):115-20.

181. Eichler Klaus, Puhan Milo A, Steurer Johann, Bachmann Lucas M. Prediction of first coronary events with the Framingham score: a systematic review. American heart journal 2007;153(5):722-31. e8.

182. Hayward Rodney A, Kent David M, Vijan Sandeep, Hofer Timothy P. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6(1):18.

183. Hughes Kenneth, Leong WP, Sothy SP, Lun KC, Yeo PPB. Relationships between cigarette smoking, blood pressure and serum lipids in the Singapore general population. International journal of epidemiology 1993;22(4):637-43.

184. Catalano M, Aronica A, Carzaniga G, Seregni R, Libretti A. Serum lipids and apolipoproteins in patients with essential hypertension. Atherosclerosis 1991;87(1):17-22.

185. Kostis W. J., Thijs L., Richart T., Kostis J. B., Staessen J. A. Persistence of mortality reduction after the end of randomized therapy in clinical trials of blood pressure-lowering medications. Hypertension 2010;56(6):1060-8.

186. Hirakawa Yoichiro, Arima Hisatomi, Rodgers Anthony, Woodward Mark, Chalmers John. Cumulative in-trial and post-trial effects of blood pressure and lipid lowering: systematic review and meta-analysis. Journal of hypertension 2017;35(5):905-13.

187. Helgeland Anders. Treatment of mild hypertension: a five year controlled drug trial: the Oslo study. The American journal of medicine 1980;69(5):725-32.

188. Nelson Mark R. a, Chowdhury Enayet K. b, Doust Jenny c, Reid Christopher M. b d, Wing Lindon M. H. e. Ten-year legacy effects of baseline

blood pressure 'treatment naivety' in the Second Australian National Blood Pressure study. Journal of Hypertension.

189. The Allhat Officers and Coordinators for the Allhat Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (allhat). JAMA 2002;288(23):2981-97.

190. Barzilay Joshua I, Davis Barry R, Pressel Sara L, Cutler Jeffrey A, Einhorn Paula T, Black Henry R, et al. Long-term effects of incident diabetes mellitus on cardiovascular outcomes in people treated for hypertension: the ALLHAT Diabetes Extension Study. Circ Cardiovasc Qual Outcomes 2012:CIRCOUTCOMES. 111.962522.

191. Vanuzzo Diego. The epidemiological concept of residual risk. Intern Emerg Med 2011;6(1):45.

192. Asayama Kei, Satoh Michihiro, Murakami Yoshitaka, Ohkubo Takayoshi, Nagasawa Sin-ya, Tsuji Ichiro, et al. Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis. Hypertension 2014;63(6):1189-97.

193. Lieb Wolfgang, Enserro Danielle M, Sullivan Lisa M, Vasan Ramachandran S. Residual Cardiovascular Risk in Individuals on Blood Pressure–Lowering Treatment. Journal of the American Heart Association 2015;4(11):e002155.

194. Joseph KS, Mehrabadi Azar, Lisonkova Sarka. Confounding by indication and related concepts. Current Epidemiology Reports 2014;1(1):1-8.

195. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. New England Journal of Medicine 2006;355(15):1551-62.

196. THE AUSTRALIAN THERAPEUTIC TRIAL IN MILD HYPERTENSION. The Lancet 1980;315(8181):1261-7.

197. Ho Chau Le Bao, Breslin Monique, Doust Jenny, Reid Christopher M, Nelson Mark R. Effectiveness of blood pressure-lowering drug treatment by

levels of absolute risk: post hoc analysis of the Australian National Blood Pressure Study. BMJ open 2018;8(3):e017723.

198. NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. New England Journal of Medicine 2010;362(16):1477-90.

199. Neaton James D, Grimm Richard H, Prineas Ronald J, Stamler Jeremiah, Grandits Greg A, Elmer Patricia J, et al. Treatment of mild hypertension study: final results. Jama 1993;270(6):713-24.

200. Ho Chau Le Bao, Sanders Sharon, Doust Jenny, Breslin Monique, Reid Christopher M, Nelson Mark Raymond. Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review. JMIR research protocols 2017;6(9).

201. Lefebvre C, Manheimer E, Glanville J. Chapter 6.4. 11.1 The Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions Version;5(0).

202. Musini Vijaya M, Gueyffier Francois, Puil Lorri, Salzwedel Douglas M, Wright James M. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Cochrane Database of Systematic Reviews 2017(8).

203. Hoes Arno W, Grobbee Diederick E, Lubsen Jacobus. Does drug treatment improve survival? Reconciling the trials in mild-to-moderate hypertension. 1995.

204. United States Public Health Hospitals Cooperative Study Group. Morbidity and mortality in mild essential hypertension. Circ Res 1972;30(31):110-21.

205. Smith W McFate. Treatment of mild hypertension: results of a ten-year intervention trial. Circ Res 1977;40(5 Suppl 1):I98-105.

206. Higgins Julian P T, Altman Douglas G, Gøtzsche Peter C, Jüni Peter, Moher David, Oxman Andrew D, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials; 2011.

207. Sterne Jonathan AC, Hernán Miguel A, Reeves Barnaby C, Savović Jelena, Berkman Nancy D, Viswanathan Meera, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj 2016;355:i4919.

208. Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016; 2016 20 April 2019]; Available from: http://www.riskofbias.info

209. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016(10 (Suppl 1)).

210. Brockhaus A Catharina, Bender Ralf, Skipka Guido. The Peto odds ratio viewed as a new effect measure. Stat Med 2014;33(28):4861-74.

211. Tierney Jayne F, Stewart Lesley A, Ghersi Davina, Burdett Sarah, Sydes Matthew R. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8(1):16.

212. The Cochrane Collaboration. Review Manager (RevMan) [Computer program],Version 5.3. Copenhagen: The Nordic Cochrane Centre; 2014.

213. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. Journal of human hypertension 1996;10(1):1-8.

214. Kostis John B, Cabrera Javier, Cheng Jerry Q, Cosgrove Nora M, Deng Yingzi, Pressel Sara L, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 2011;306(23):2588-93.

215. Staessen Jan A, Thijs Lutgarde, Fagard Robert, Celis Hilde, Birkenhäger Willem H, Bulpitt Christopher J, et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. Journal of hypertension 2004;22(4):847-57.

216. Group Veterans Administration Cooperative Study, Agents On Antihypertensive. Effects of treatment on morbidity in hypertension: II. Results

in patients with diastolic blood pressure averaging 90 to 140 mmHg. JAMA 1970;213:l.

217. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of Treatment on Morbidity in Hypertension: III. Influence of Age, Diastolic Pressure, and Prior Cardiovascular Disease; Further Analysis of Side Effects. Circulation 1972;45(5):991-1004.

218. Perry HM, Goldman Anne I, Lavin Mary Ann, Schnaper Harold W, Fitz Annette E, Frohlich Edward D, et al. Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Ann NY Acad Sci 1978;304:267-88.

219. Perry Jr HM. Treatment of mild hypertension. Preliminary results of a two-year feasibility trial. Circ Res 1977;40(5 Suppl 1):I180-7.

220. Party Medical Research Council Working. MRC trial of treatment of mild hypertension: principal results. British Medical Journal (Clinical Research Edition) 1985:97-104.

221. BRENNAN PJ. CORONARY HEART-DISEASE IN THE MEDICAL-RESEARCH-COUNCIL TRIAL OF TREATMENT OF MILD HYPERTENSION. Br Heart J 1988;59(3):364-78.

222. Investigators* SOLVD. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. New England Journal of Medicine 1992;327(10):685-91.

223. Jong Philip, Yusuf Salim, Rousseau Michel F., Ahn Sylvie A., Bangdiwala Shrikant I. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. The Lancet 2003;361(9372):1843-8.

224. Elmer Patricia J, Grimm Richard, Laing Brian, Grandits Greg, Svendsen Ken, Vanheel Nancy, et al. Lifestyle intervention: results of the Treatment of Mild Hypertension Study (TOMHS). Prev Med 1995;24(4):378-88.

225. Pocanic D. [Ten years after publishing results from The Heart Outcomes Prevention Evaluation Study--HOPE: implications on treatment with

angiotensin converting enzyme inhibitors in clinical practice]. Lijecnicki Vjesnik 2011;133(1-2):69-71.

226. Bosch J, Lonn E, Pogue J, Arnold Jm, Dagenais Gr, Yusuf S. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation [serial online] 2005;112(9):1339-46. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/037/CN-00552037/frame.html

http://circ.ahajournals.org/content/circulationaha/112/9/1339.full.pdf.

227. Investigators Heart Outcomes Prevention Evaluation Study. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. New England Journal of Medicine 2000;342(3):145-53.

228. Appel Lj, Wright Jt, Greene T, Kusek Jw, Lewis Jb, Wang X, et al. Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. Archives of internal medicine [serial online] 2008;168(8):832-9. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/266/CN-00639266/frame.html

https://jamanetwork.com/journals/jamainternalmedicine/articlepdf/414567/ioi70267_832_839.pdf.

229. Appel L. J., Wright Jr J. T., Greene T., Agodoa L. Y., Astor B. C., Bakris G. L., et al. Intensive blood-pressure control in hypertensive chronic kidney disease. New England Journal of Medicine 2010;363(10):918-29.

230. Wright Jr Jackson T, Bakris George, Greene Tom, Agodoa Larry Y, Appel Lawrence J, Charleston Jeanne, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. Jama 2002;288(19):2421-31.

231. Ruggenenti Piero, Fassi Anna, Ilieva Anelja Parvanova, Bruno Simona, Iliev Ilian Petrov, Brusegan Varusca, et al. Preventing microalbuminuria in type 2 diabetes. New England Journal of Medicine 2004;351(19):1941-51.

232. Ruggenenti Piero, Porrini Esteban, Motterlini Nicola, Perna Annalisa, Ilieva Aneliya Parvanova, Iliev Ilian Petrov, et al. Measurable Urinary Albumin Predicts Cardiovascular Risk among Normoalbuminuric Patients with Type 2 Diabetes. Journal of the American Society of Nephrology : JASN 2012;23(10):1717-24.

233. Porrini E., Ruggenenti P., Motterlini N., Perna A., Ilieva A. P., Iliev I. P., et al. 10-year cardiovascular risk in type 2 diabetes is predicted by measurable urinary albumin even in the normoalbuminuric range. Nephrology Dialysis Transplantation 2012;27:ii55-ii6.

234. Ostroumova O. D., Zykova A. A. [The Results of Long-Term Observation of Patients Who Participated in the ADVANCE Trial]. Kardiologiia 2015;55(11):94-100.

235. Ohkuma T., Woodward M., Jun M., Muntner P., Hata J., Colagiuri S., et al. Prognostic Value of Variability in Systolic Blood Pressure Related to Vascular Events and Premature Death in Type 2 Diabetes Mellitus: The ADVANCE-ON Study. Hypertension 2017;70(2):461-8.

236. Zoungas S., Chalmers J., Neal B., Billot L., Li Q., Biostat M., et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. New England Journal of Medicine 2014;371(15):1392-406.

237. Patel Anushka. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. The Lancet 2007;370(9590):829-40.

238. Kanorskii S. G. ADVANCE-ON Trial; How to Achieve Maximum Reduction of Mortality in Patients With Type 2 Diabetes. [Russian]. Kardiologiia 2015;55(2):96-101.

239. Ogihara T., Fujimoto A., Ueshima K., Nakao K., Saruta T. Optimal blood pressure to prevent cardiovascular events in the elderly high-risk hypertensive patients: Subanalysis of the CASE-J Ex study. Journal of Hypertension 2012;30:e244-e5.

240. Ogihara T, Ueshima K, Nakao K, Fukiyama K, Oba K, Yasuno S, et al. Long-term effects of candesartan and amlodipine on cardiovascular morbidity and mortality in Japanese high-risk hypertensive patients: the Candesartan Antihypertensive Survival Evaluation in Japan Extension Study (CASE-J Ex). Hypertension research : official journal of the Japanese Society of Hypertension [serial online] 2011;34(12):1295-301. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/786/CN-00860786/frame.html

http://www.nature.com/articles/hr2011120.pdf.

241. Nakao K., Ogihara T., Matsuoka H., Oba K., Yasuno S., Fujimoto A., et al. Long-term effects of candesartan and amlodipine on cardiovascular events in high-risk hypertensive patients: Results of case-J extension. Journal of Hypertension 2010;28:e248.

242. Ogihara Toshio, Nakao Kazuwa, Fukui Tsuguya, Fukiyama Kohshiro, Ueshima Kenji, Oba Koji, et al. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension 2008;51(2):393-8.

243. Holman Rr, Paul Sk, Bethel Ma, Neil Ha, Matthews Dr. Long-term follow-up after tight control of blood pressure in type 2 diabetes. New England journal of medicine [serial online] 2008;359(15):1565-76. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/024/CN-00651024/frame.html

http://www.nejm.org/doi/pdf/10.1056/NEJMoa0806359.

244. Wan He; Daniel Goodkind; and Paul Kowal. U.S. Census Bureau. International Population Reports, P95/16-1, An Aging World: 2015,. U.S. Government Publishing Office, Washington, DC,; 2016.

245. Prince Martin J., Wu Fan, Guo Yanfei, Gutierrez Robledo Luis M., O'Donnell Martin, Sullivan Richard, et al. The burden of disease in older people and implications for health policy and practice. The Lancet;385(9967):549-62.

246. Baigent Colin, Keech A, Kearney PM, Blackwell L. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. The Lancet 2005;366(9493):1267.

247. Cholesterol Treatment Trialists Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. The Lancet 2012;380(9841):581-90.

248. Morgan T. K., Williamson M., Pirotta M., Stewart K., Myers S. P., Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust 2012;196(1):50-3.

249. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. NCHS data brief, no 177. Hyattsville, MD: National Center for Health Statistics; 2014.

250. Afilalo J., Duque G., Steele R., Jukema J. W., de Craen A. J., Eisenberg M. J. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol 2008;51(1):37-45.

251. Hunt David, Young Peta, Simes John, Hague Wendy, Mann Stewart, Owensby Dwain, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. Ann Intern Med 2001;134(10):931-40.

252. Miettinen Tatu A, Pyörälä Kalevi, Olsson Anders G, Musliner Thomas A, Cook Thomas J, Faergeman Ole, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris. Circulation 1997;96(12):4211-8.

253. Lewis Sandra J, Moye Lemuel A, Sacks Frank M, Johnstone David E, Timmis Gerald, Mitchell Jayne, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the

average range: results of the Cholesterol and Recurrent Events (CARE) trial. Ann Intern Med 1998;129(9):681-9.

254. Downs John R, Clearfield Michael, Weis Stephen, Whitney Edwin, Shapiro Deborah R, Beere Polly A, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Jama 1998;279(20):1615-22.

255. Redberg R. F., Katz M. H. Statins for primary prevention: The debate is intense, but the data are weak. JAMA 2016;316(19):1979-81.

256. Curfman G. Risks of statin therapy in older adults. JAMA Internal Medicine 2017;177(7):966-.

257. Gurwitz J. H., Go A. S., Fortmann S. P. Statins for primary prevention in older adults: Uncertainty and the need for more evidence. JAMA 2016;316(19):1971-2.

258. Waters David D. Meta-Analyses of Statin Trials. Journal of the American College of Cardiology; 2013.

259. Armitage Jane, Baigent Colin, Barnes Elizabeth, Betteridge D John, Blackwell Lisa, Blazing Michael, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. The Lancet 2019;393(10170):407-15.

260. Furberg Curt D, Wright Jackson T, Davis Barry R, Cutler Jeffrey A, Alderman Michael, Black Henry, et al. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J Am Med Assoc 2002;288(23):2998-3007.

261. Lemaitre R. N., Psaty B. M., Heckbert S. R., Kronmal R. A., Newman A. B., Burke G. L. Therapy with hydroxymethylglutaryl coenzyme a reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults: Evidence from the cardiovascular health study. Archives of Internal Medicine 2002;162(12):1395-400.

262. Alpérovitch Annick, Kurth Tobias, Bertrand Marion, Ancelin Marie-Laure, Helmer Catherine, Debette Stéphanie, et al. Primary prevention with lipid

lowering drugs and long term risk of vascular events in older people: population based cohort study. BMJ 2015;350.

263. Fried T. R., Tinetti M. E., Towle V., O'Leary J. R., Iannone L. Effects of benefits and harms on older persons; willingness to take medication for primary cardiovascular prevention. Archives of Internal Medicine 2011;171(10):923-8.

264. Albarqouni Loai, Doust Jenny, Glasziou Paul. Patient preferences for cardiovascular preventive medication: a systematic review. Heart 2017:heartjnl-2017-311244.

265. Wing Lindon M.H., Reid Christopher M., Ryan Philip, Beilin Lawrence J., Brown Mark A., Jennings Garry L.R., et al. A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly. New England Journal of Medicine 2003;348(7):583-92.

266. Sever Peter S., Chang Choon L., Gupta Ajay K., Whitehouse Andrew, Poulter Neil R. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. European Heart Journal 2011;32(20):2525-32.

267. Nielsen Sune F., Nordestgaard Børge G., Bojesen Stig E. Statin Use and Reduced Cancer-Related Mortality. New England Journal of Medicine 2012;367(19):1792-802.

268. Platz Elizabeth A., Leitzmann Michael F., Visvanathan Kala, Rimm Eric B., Stampfer Meir J., Willett Walter C., et al. Statin Drugs and Risk of Advanced Prostate Cancer. JNCI: Journal of the National Cancer Institute 2006;98(24):1819-25.

269. Cholesterol Treatment Trialists. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7(1):e29849.

270. Nelson Mark R, Reid Chris M, Krum Henry, Muir Tui, Ryan Philip, McNeil John J. Predictors of normotension on withdrawal of antihypertensive drugs in elderly patients: prospective study in second Australian national blood pressure study cohort. Bmj 2002;325(7368):815.

271. van der Wardt Veronika, Harrison Jennifer K, Welsh Tomas, Conroy Simon, Gladman John. Withdrawal of antihypertensive medication: a systematic review. Journal of hypertension 2017;35(9):1742.

272. Nelson Mark, Reid Christopher, Krum Henry, McNeil John. A systematic review of predictors of maintenance of normotension after withdrawal of antihypertensive drugs. Am J Hypertens 2001;14(2):98-105.

273. Luymes Clare H, Poortvliet Rosalinde KE, van Geloven Nan, de Waal Margot WM, Drewes Yvonne M, Blom Jeanet W, et al. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice–the ECSTATIC study: a cluster randomised non-inferiority trial. BMC Med 2018;16(1):5.

274. Kostis John B, Espeland Mark A, Appel Lawrence, Johnson Karen C, Pierce June, Wofford James L. Does withdrawal of antihypertensive medication increase the risk of cardiovascular events? The American journal of cardiology 1998;82(12):1501-8.

275. McGrath Emer R, Beiser Alexa S, DeCarli Charles, Plourde Kendra L, Vasan Ramachandran S, Greenberg Steven M, et al. Blood pressure from mid- to late life and risk of incident dementia. Neurology 2017;89(24):2447-54.

276. STAREE Study Investigators. A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE). Clinical Trials. gov website [consultado 1 Oct 2014]. http://clinicaltrials. gov/show/NCT02099123.